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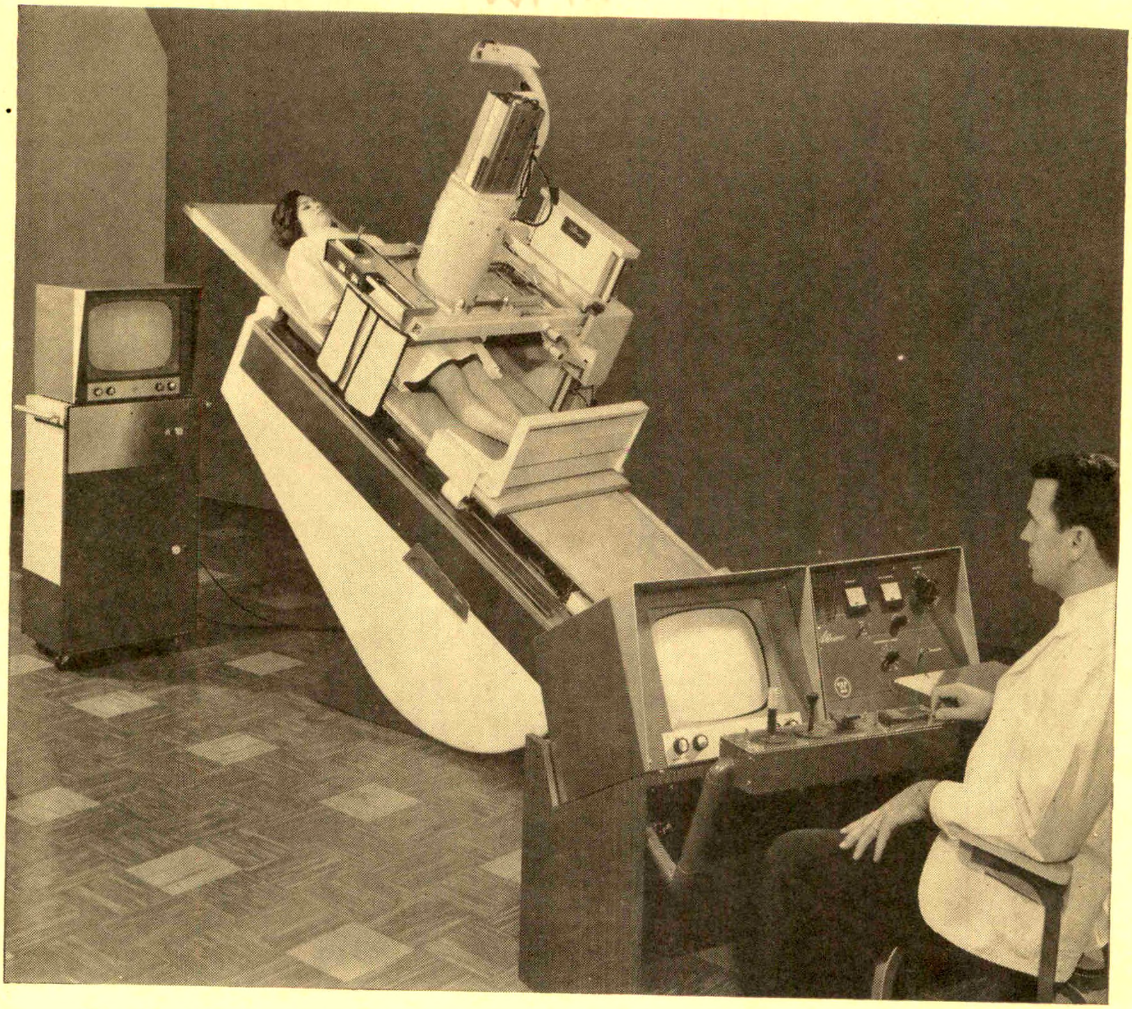

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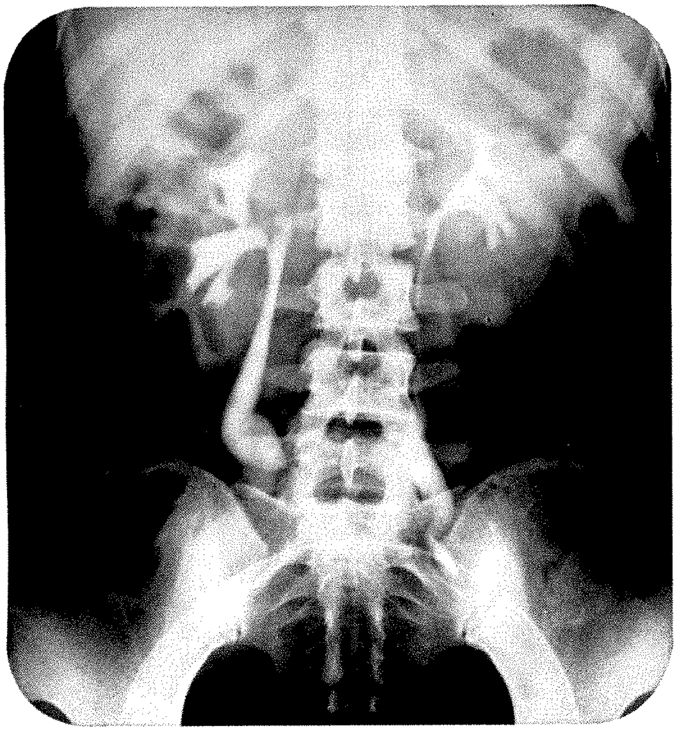

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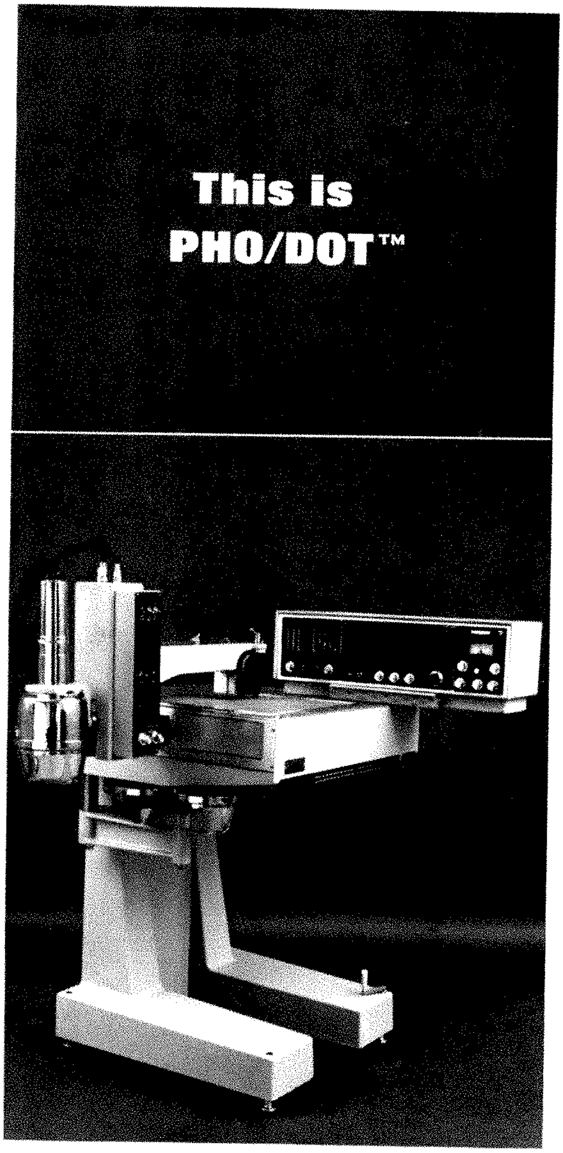

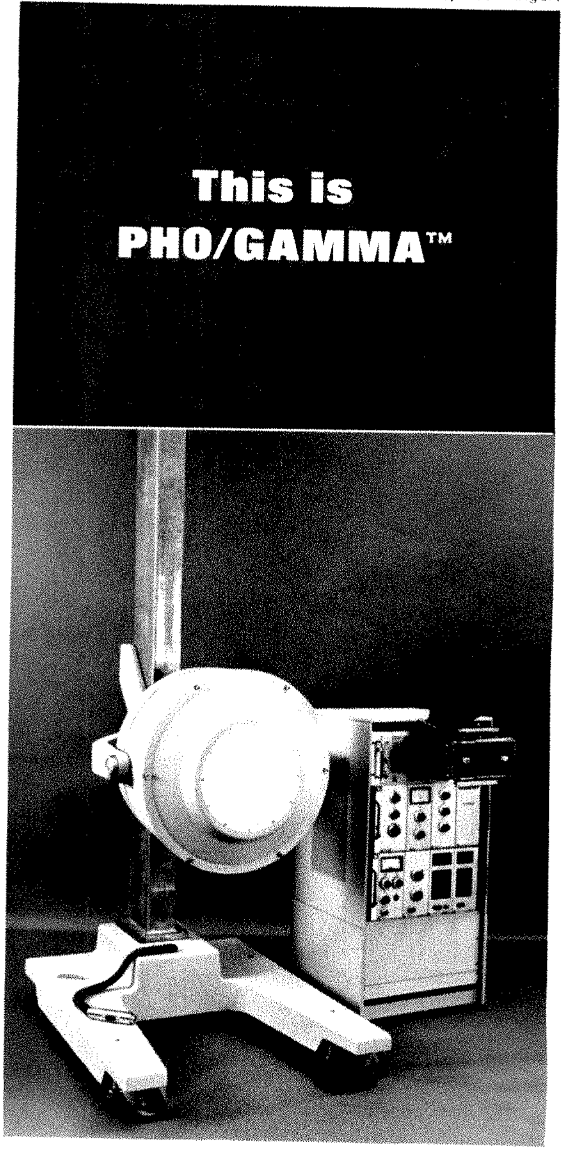

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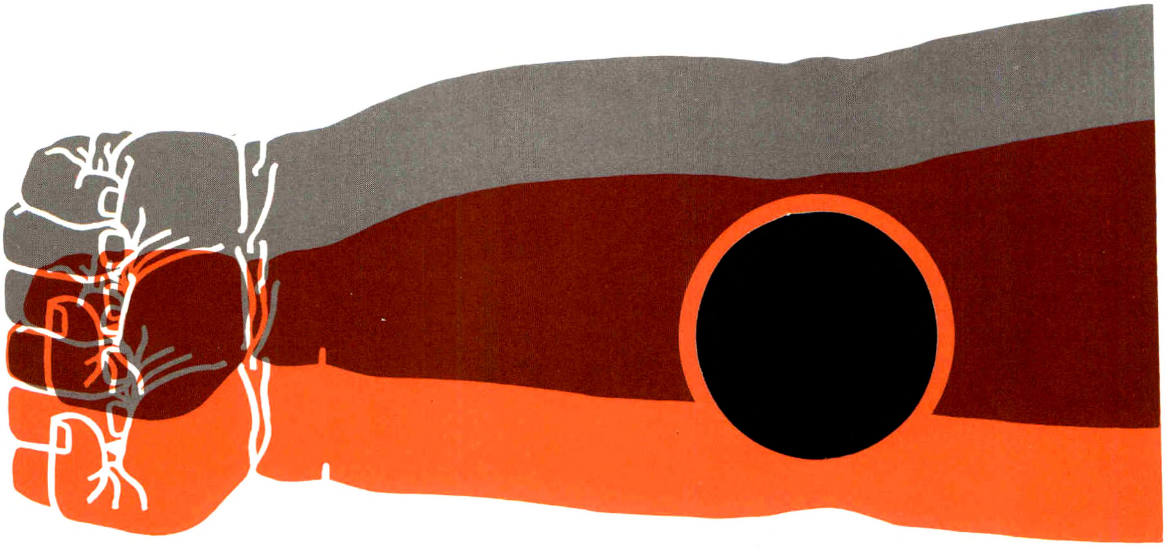

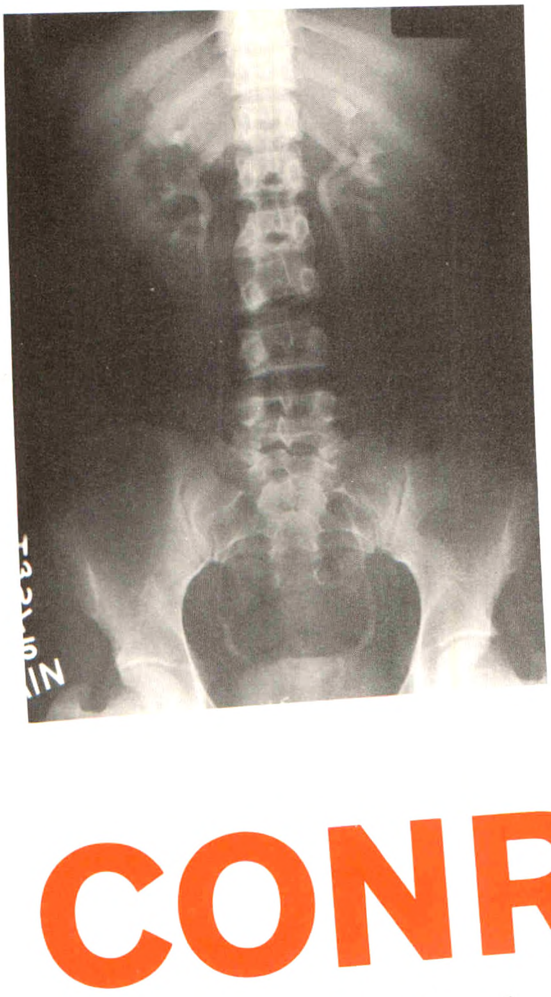

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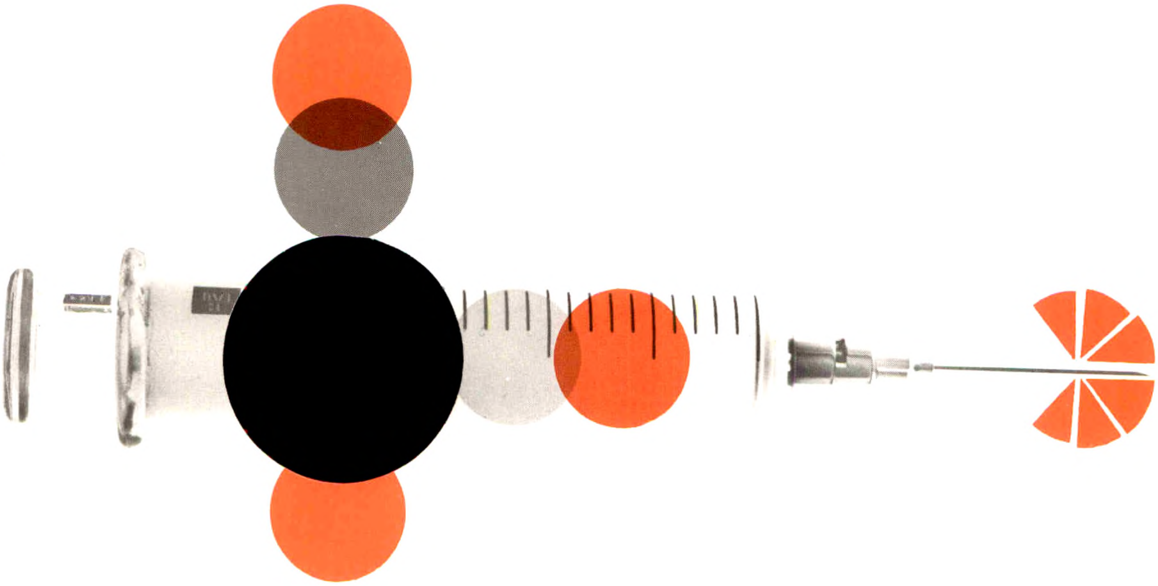

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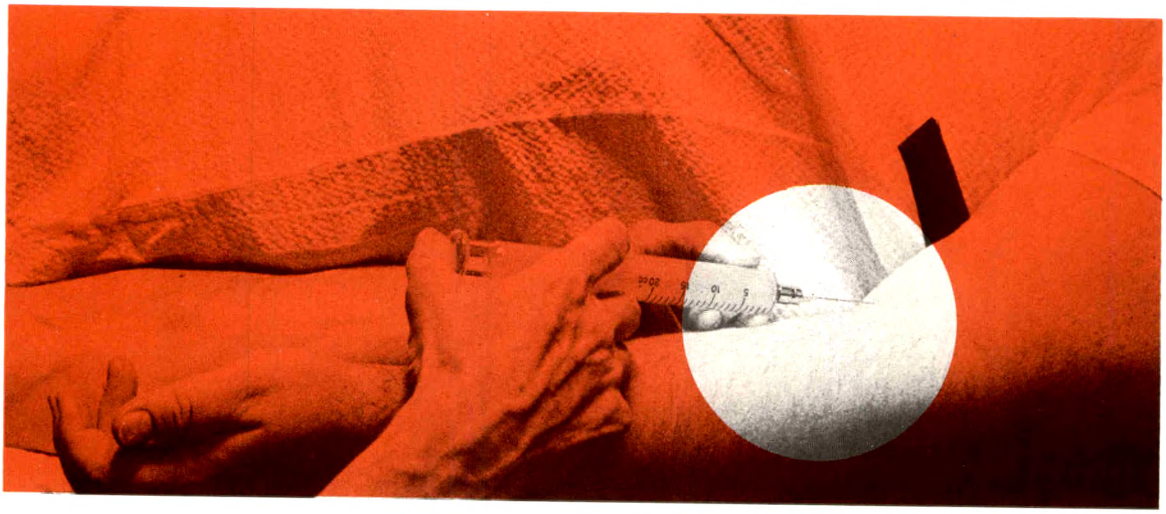

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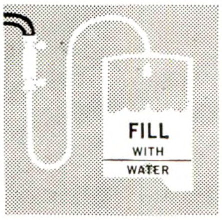
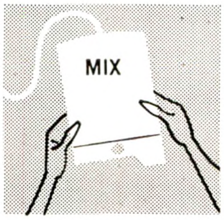


1 Connect to water tap with tubing. Add small amount hot water. Mix. Add water to desired density.



2 Mix thoroughly for about 30 seconds. Disconnect from water tap. Bleed air and water from system.

3 Add air or CO^2 if double contrast exam is desired. Clamp tubing with hemostat. Administer enema.

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1. Meyers, P. H.: J.A.M.A. 173: 1589, August 6, 1960. 2. Nathan, M. H.: Am. J. Roentgenol., Rad. Ther. and Nuclear Med. 81: 650, 1959. 3. Steinbach, H. L., et al.: J.A.M.A. 174: 1207, Oct. 29, 1960 4. Pochaczevsky, R., et al.: Radiology 77: 831, (Nov.) 1961.

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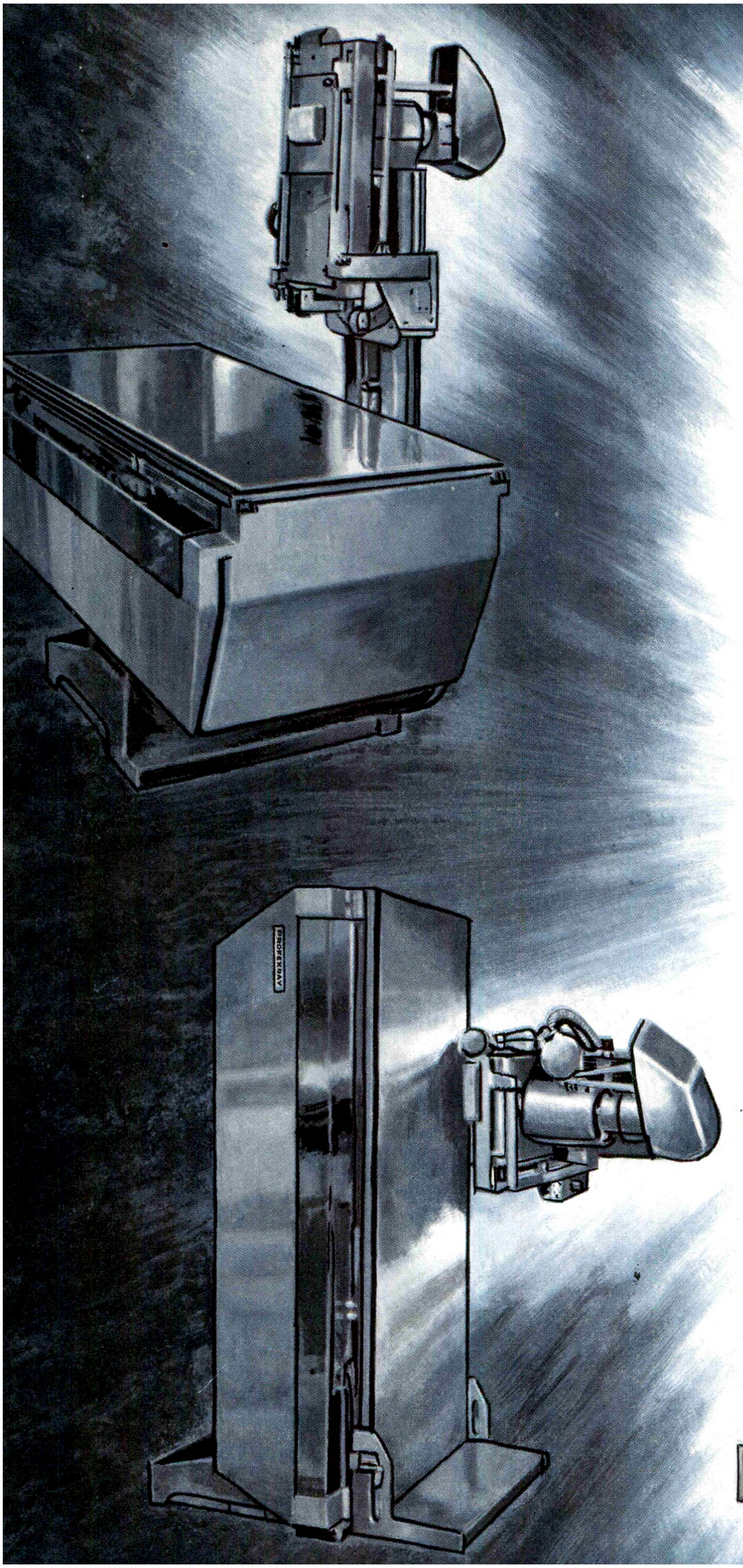

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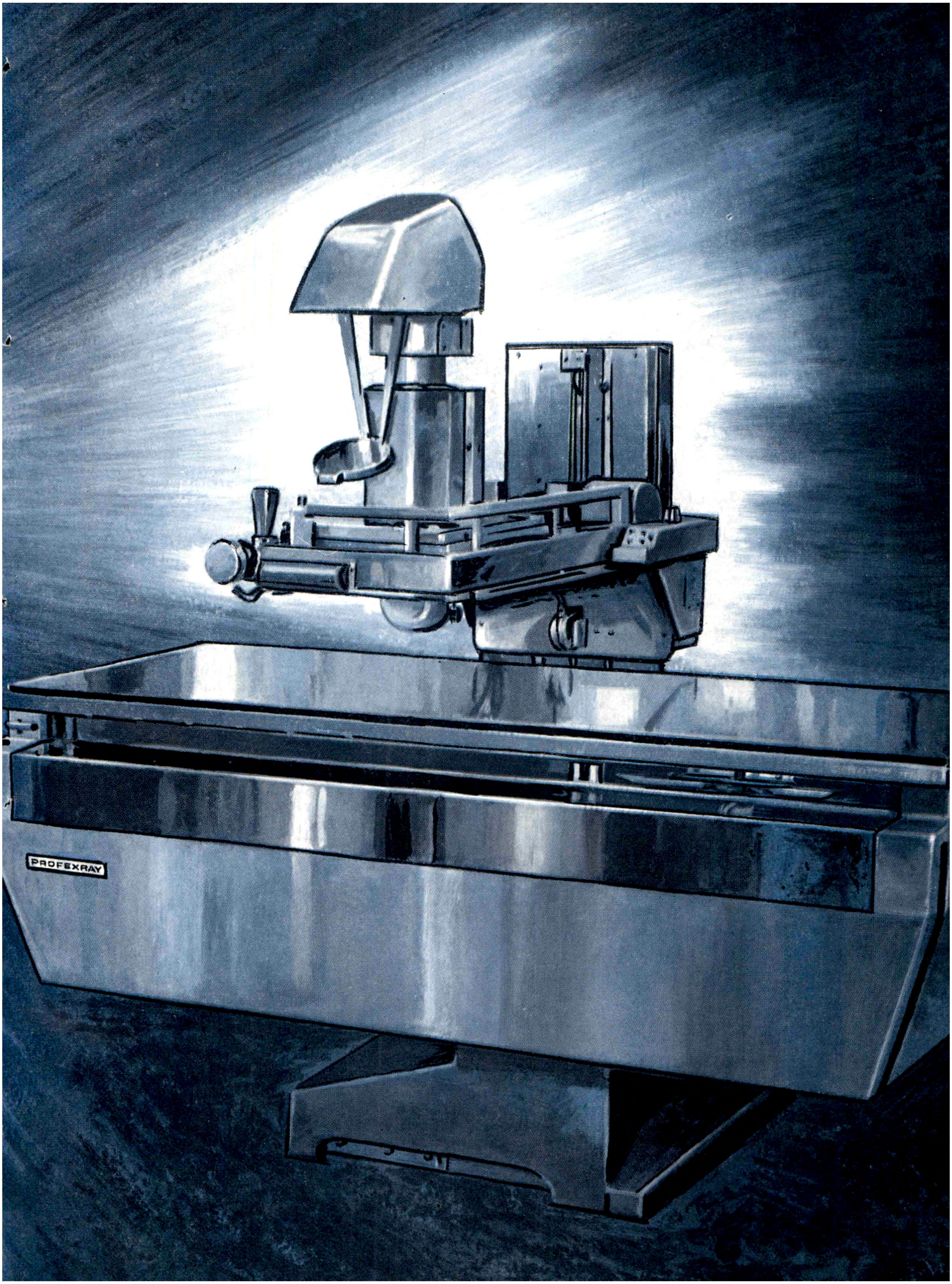
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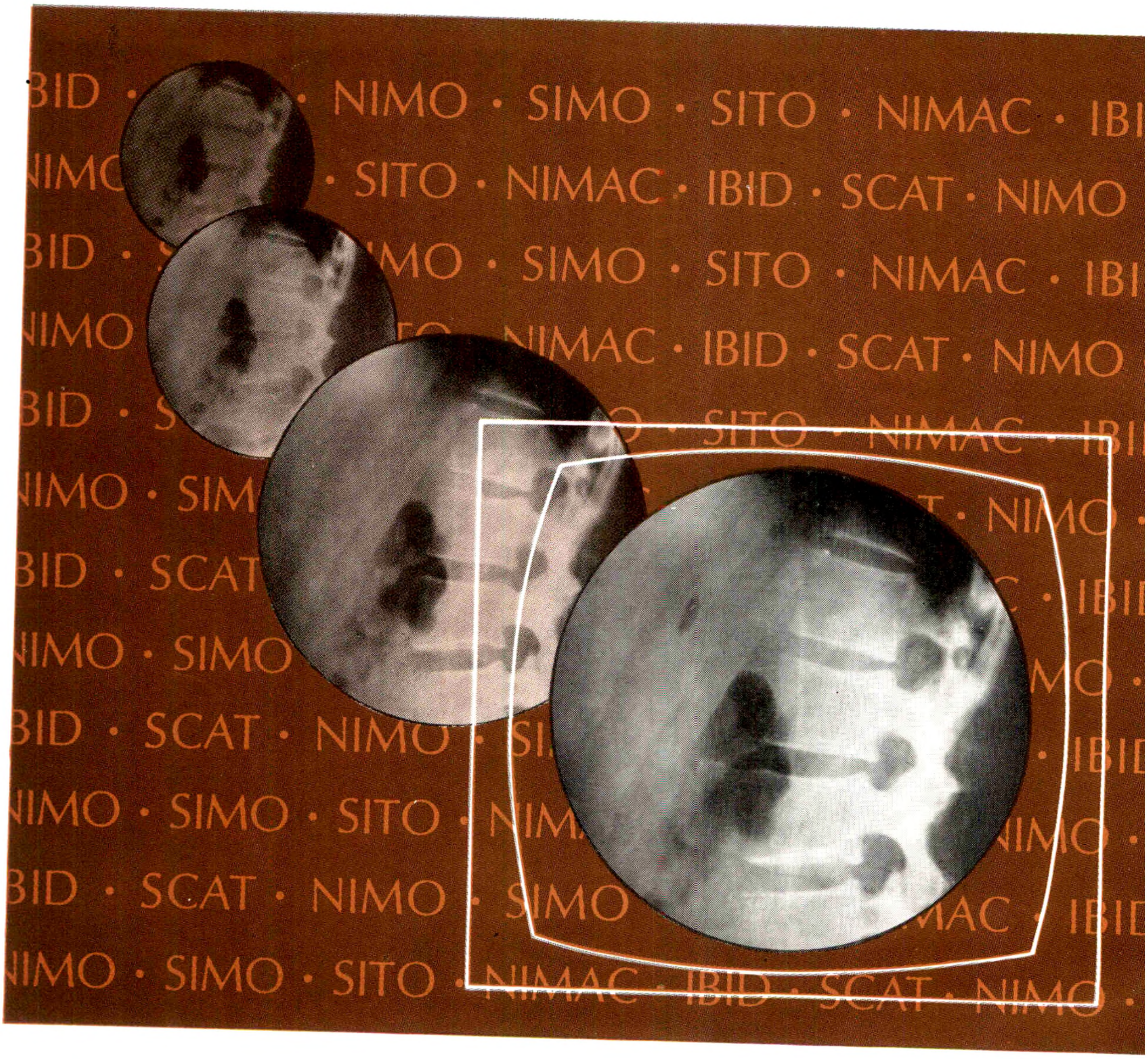

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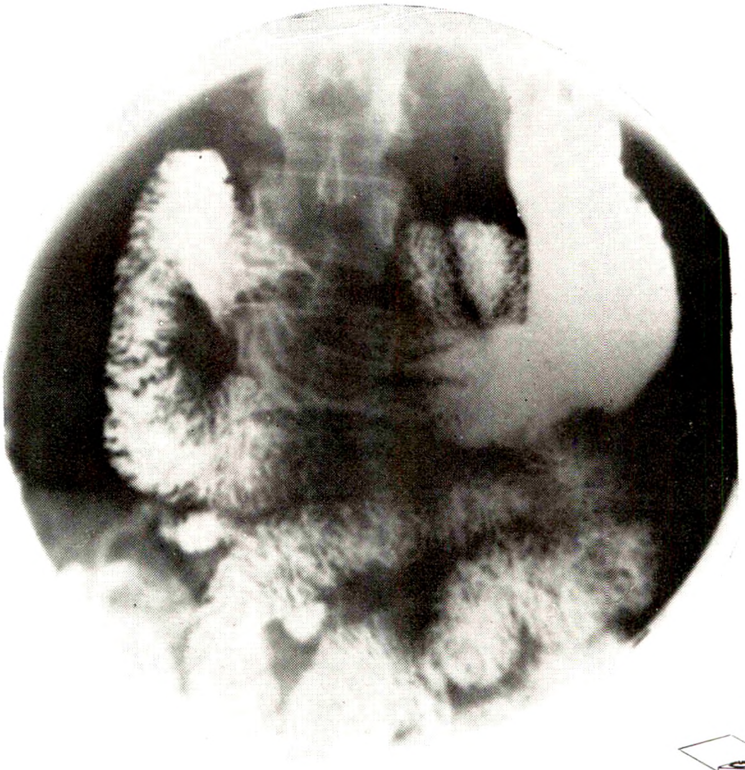

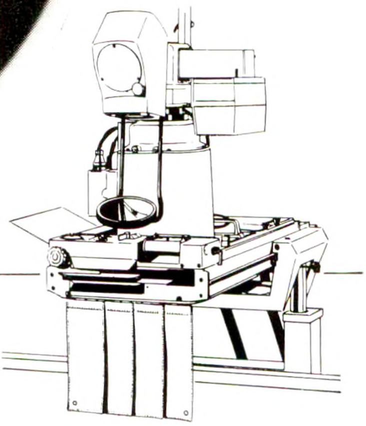

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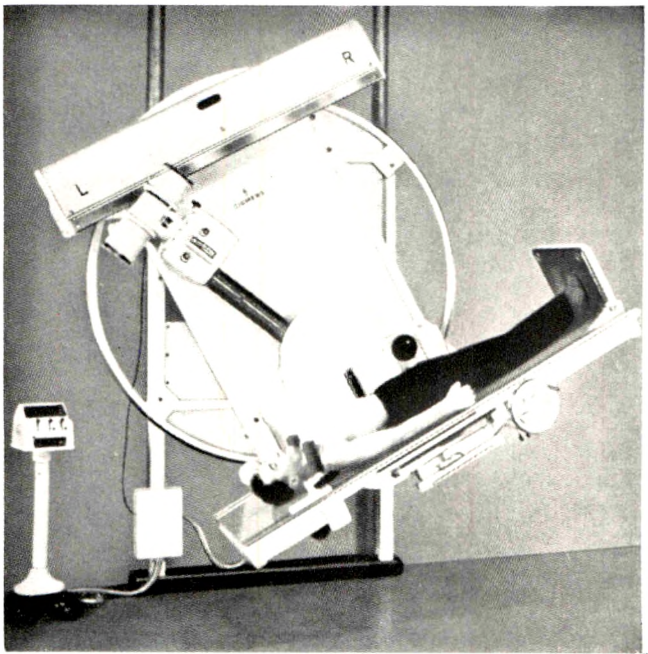

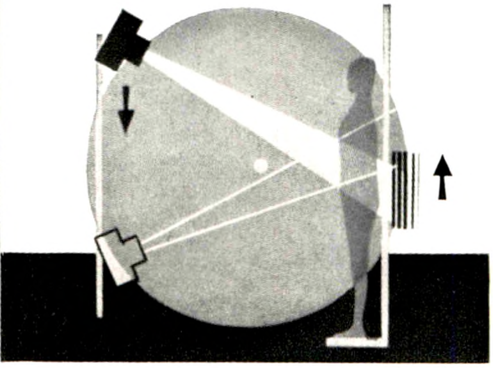

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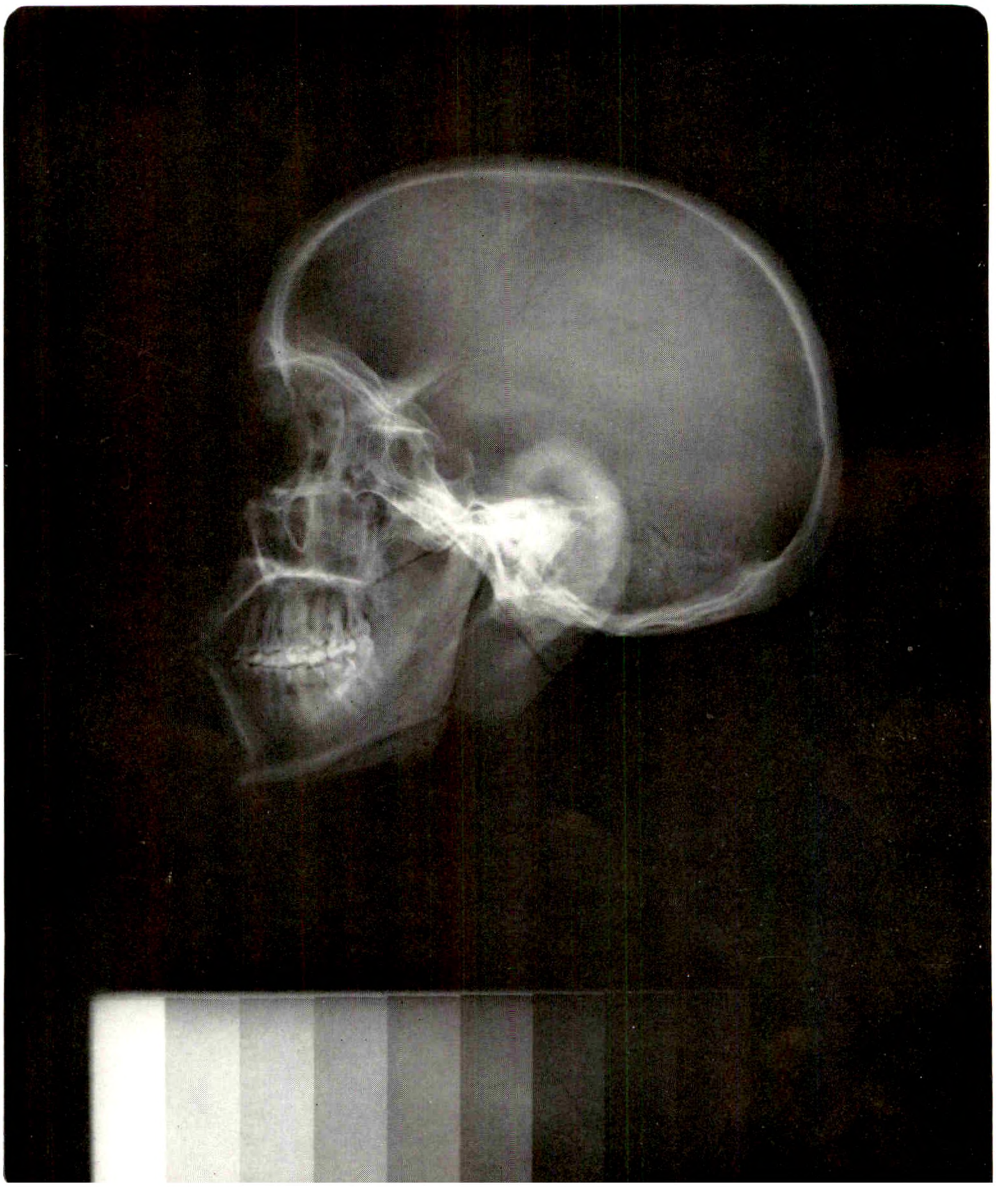

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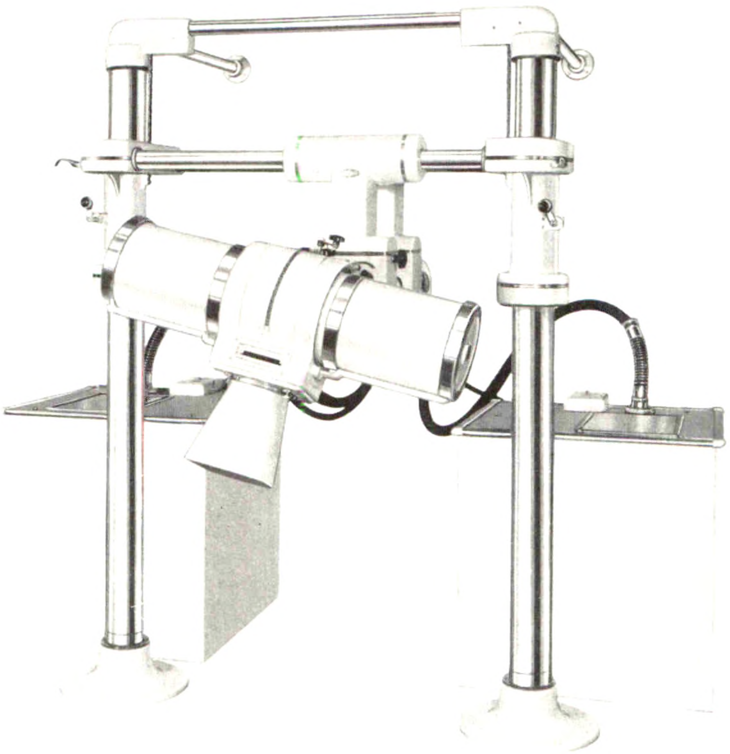

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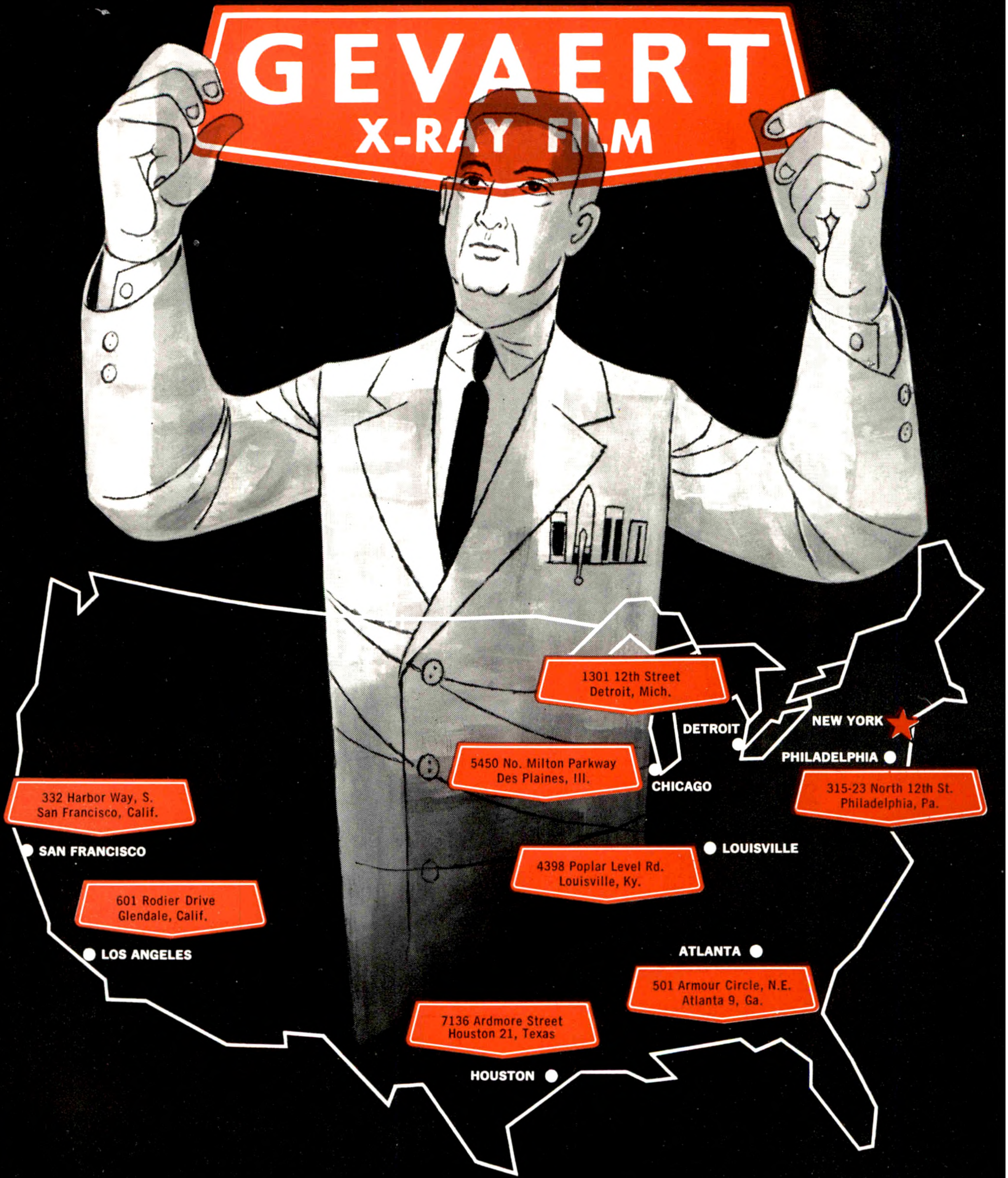

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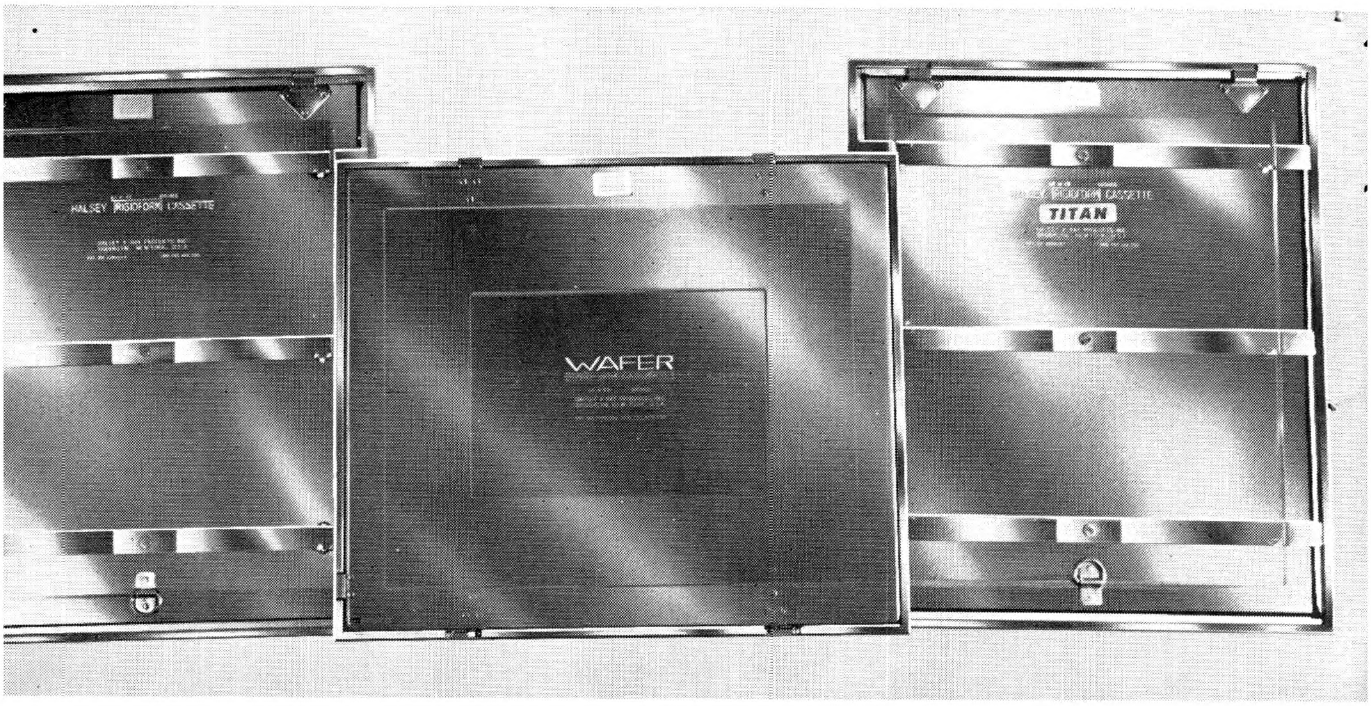

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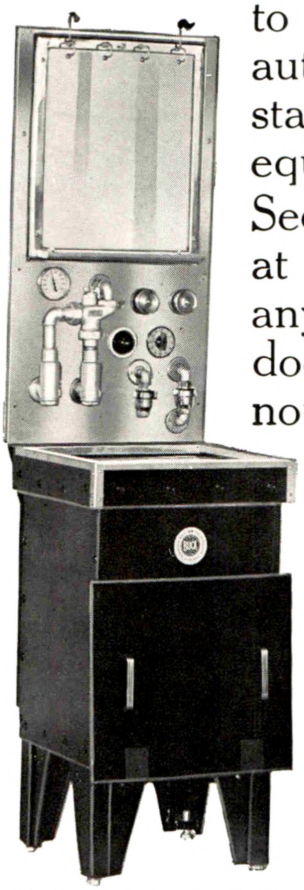

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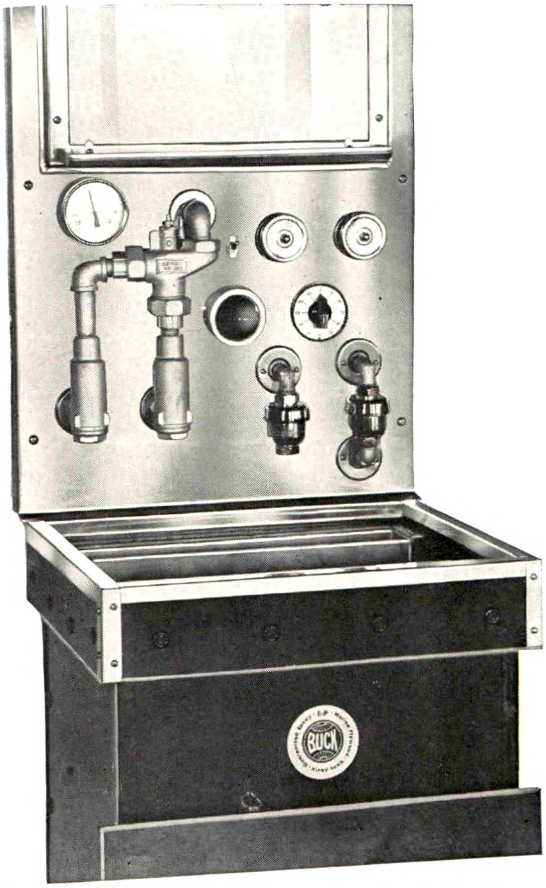

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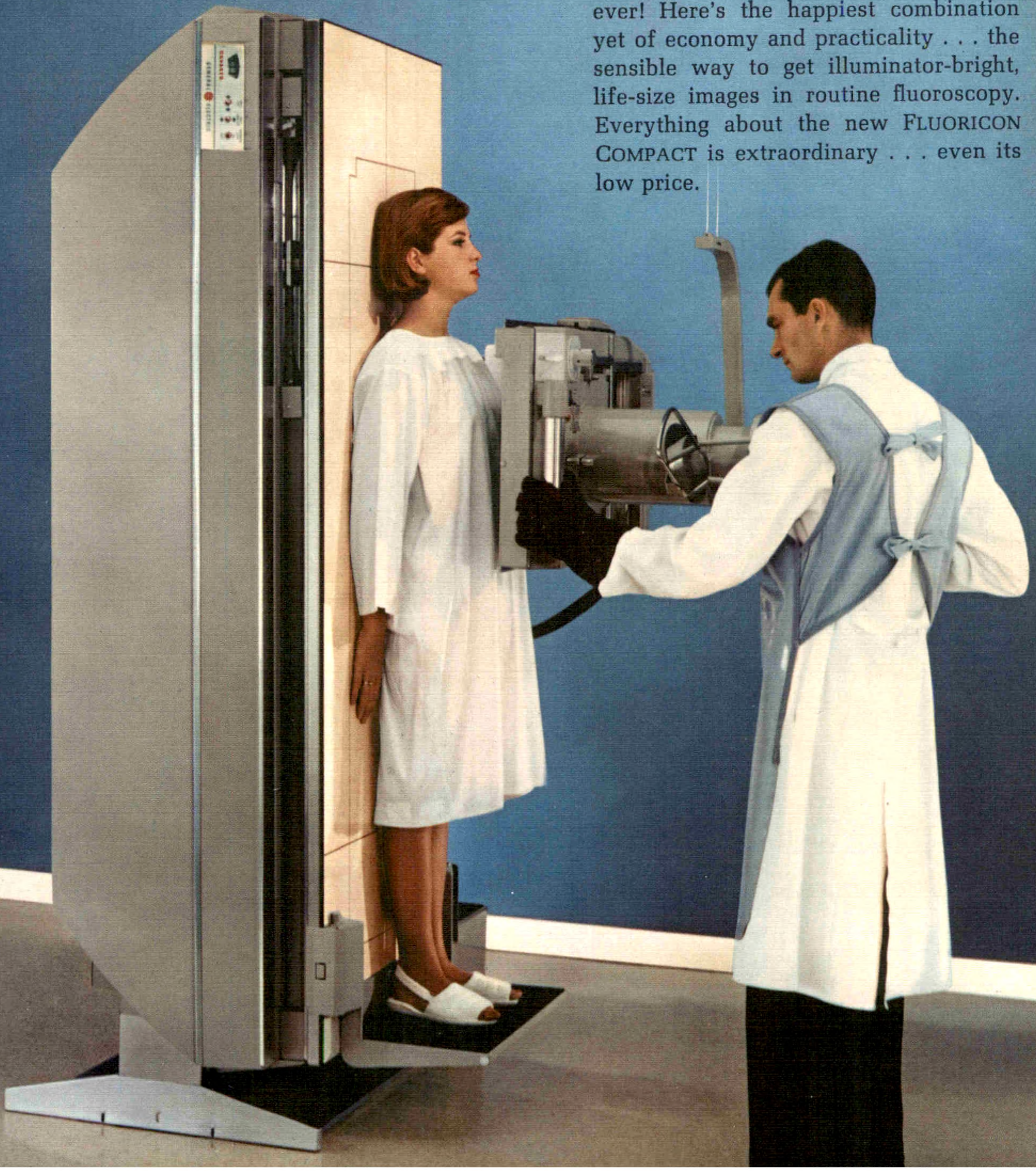

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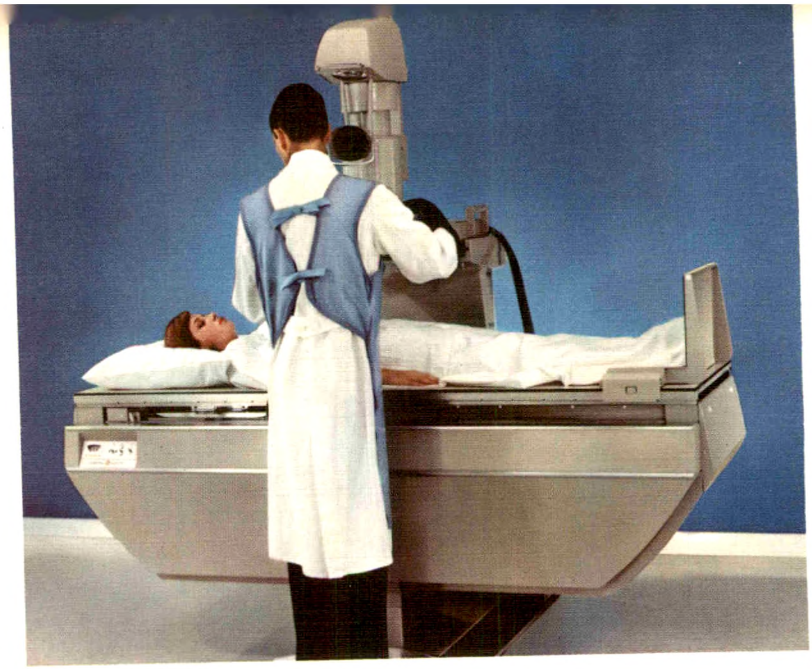

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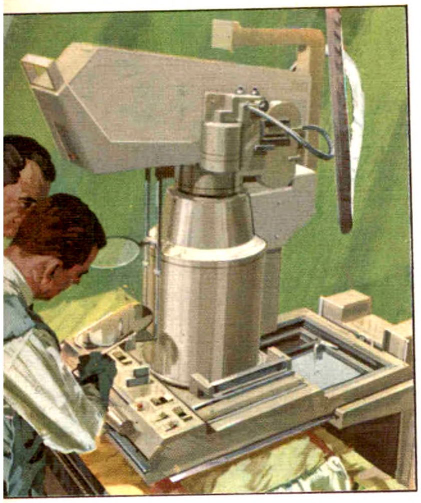

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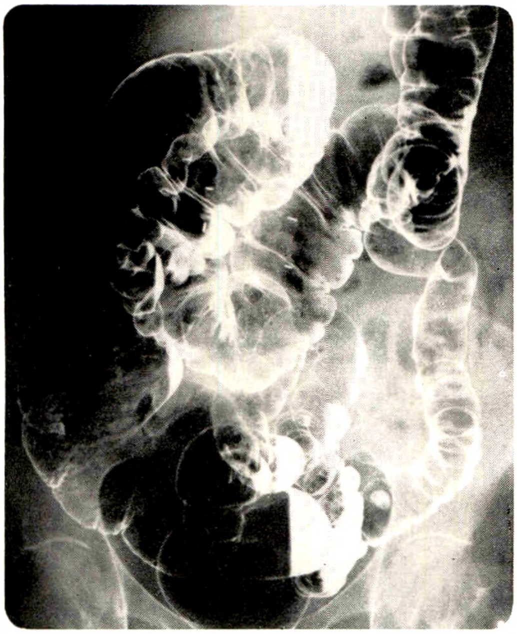

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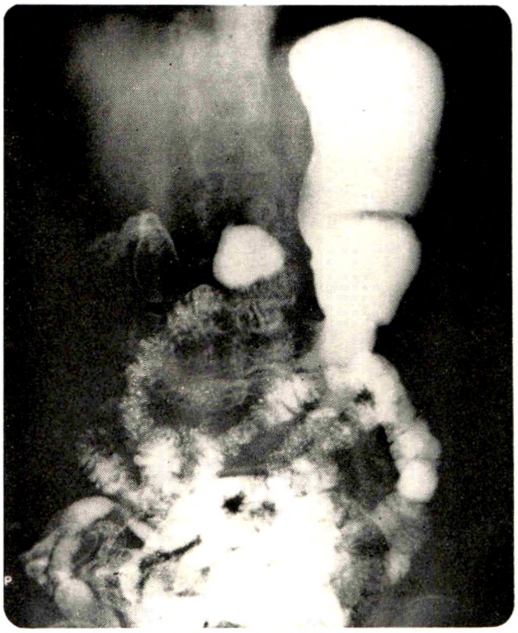

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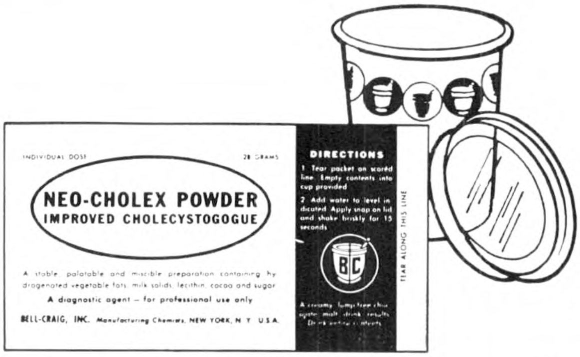
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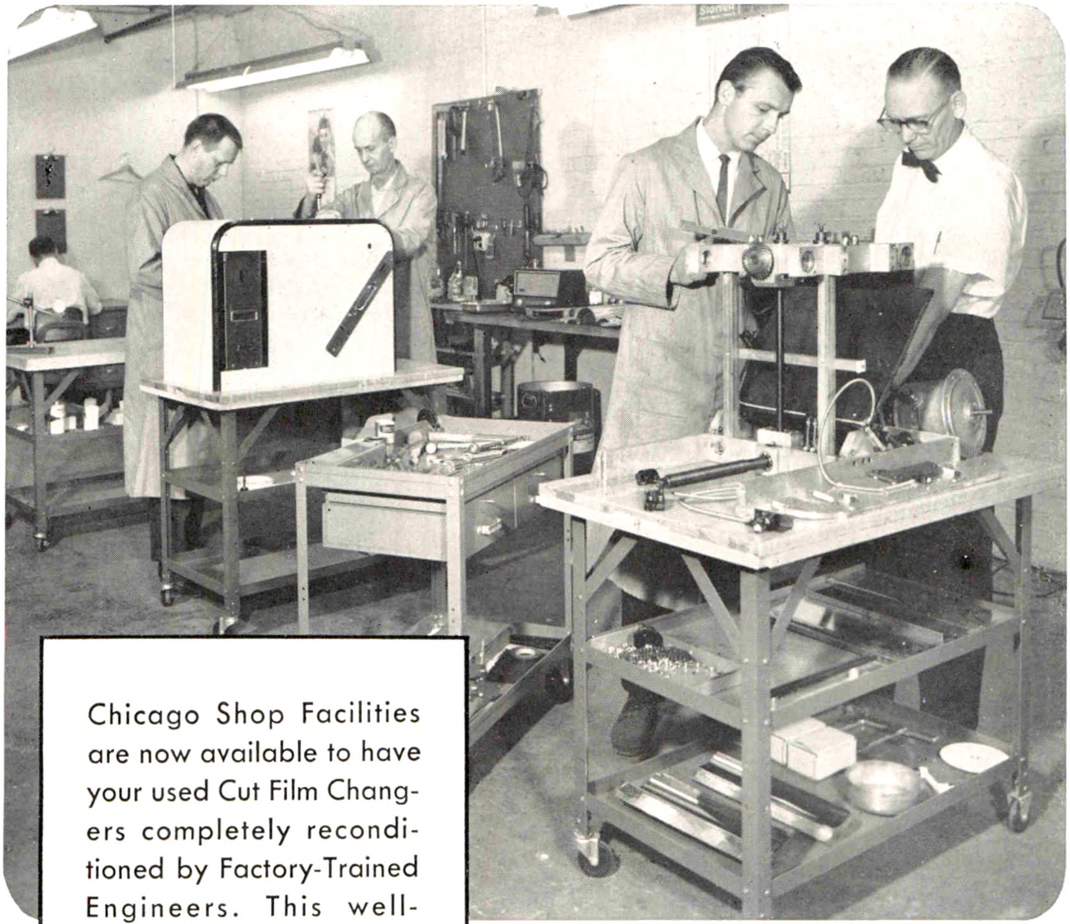

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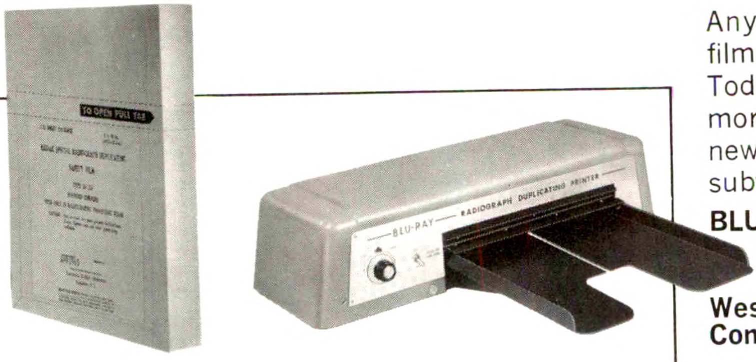

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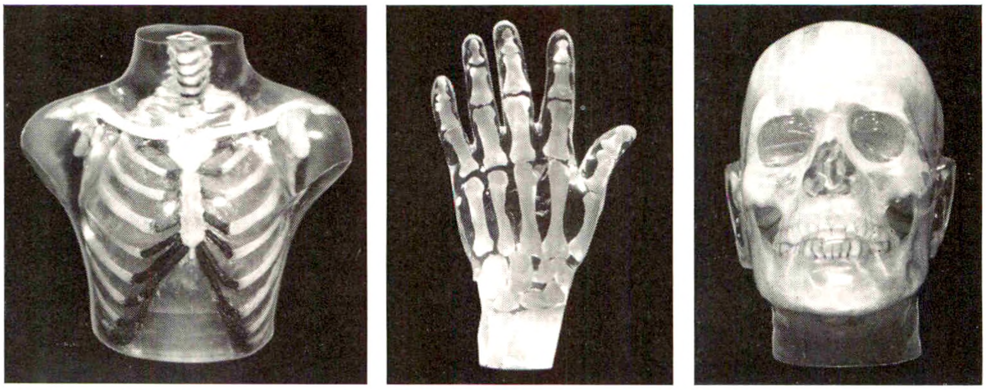

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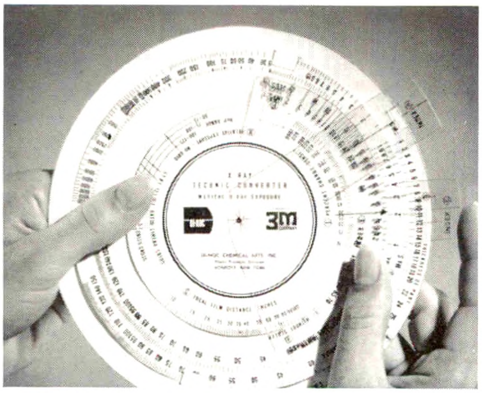

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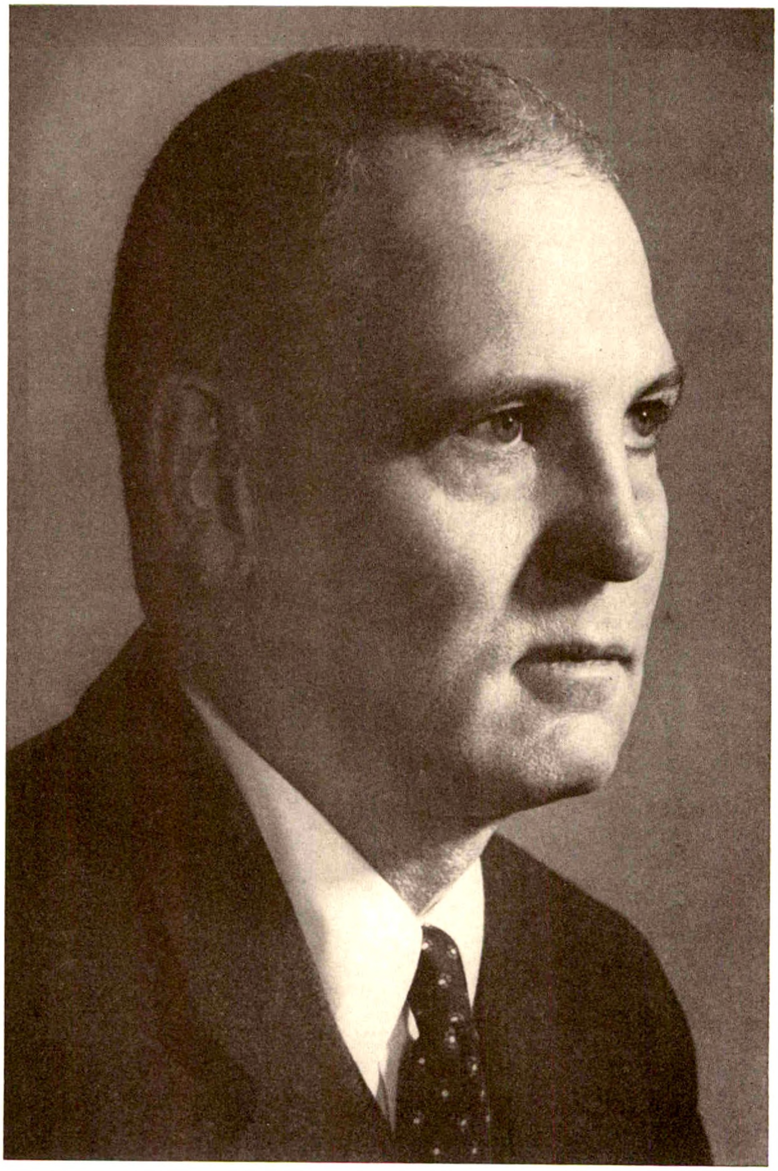

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VOL. 93 JANUARY, 1965 No. 1

CANCER MANAGEMENT AND RADIOTHERAPY CENTERS*

THE PRESIDENT'S ADDRESS, 1964

By CHARLES G. STETSON, M.D.
NEW YORK, NEW YORK

ONE of the more encouraging aspects of the cancer problem relates to the increasing cooperative effort among the various disciplines concerned with the care of the cancer patient. In reviewing the papers presented at our recent meetings and to be presented at this meeting, I am impressed by the number of communications which pertain to the combined treatment of many types of neoplasms. This trend is gratifying and is an excellent example of integrated team work which is increasing the survival and cure rates of patients with cancer. To this Society it means that a long step forward has been taken toward the fulfillment of one of its objectives, namely "to encourage liaison among various specialties concerned with the treatment of cancer." In his Presidential Address to this Society at the time of the 1962 Annual Meeting, Dr. Robert L. Brown[2] stressed that "Radiologists need to know what surgery can do and surgeons need to know what radiation can do, and they need to explore more completely the possibilities of combined therapy." Happily, it would appear that in many areas, these concepts have been accepted and are being implemented.

While it is true that we are making progress in our many excellent oncologic centers, where specialized equipment and personnel are available, there are many rural, suburban, and urban areas in which the management of the cancer patient leaves something to be desired. Everyone who falls prey to this dread disease deserves to receive the best treatment currently available and I am of the persuasion that this can be accomplished within the framework of our free enterprise system.

Statistics supplied to me by the American Cancer Society reveal that each year 40 per cent of new cancer patients are treated in hospitals of less than 150 beds. Many of these patients with certain types of cancer receive excellent care but, for others, there is a lack of availability of highly skilled cancer surgeons, pathologists, radiotherapists, and supervoltage radiation equipment. With these thoughts in mind, I would like to explore some of the possible solutions to the problem of bringing better care to more people. First, many more cancer treatment centers need to be established on a voluntary basis in our urban areas. The development of specialized cancer facilities must be a cooperative venture among groups of hospitals, and this applies to some of the surgical specialties as well as to radiotherapy centers. In many parts of the country, there has been a tendency among hospitals to duplicate expensive facilities, which has resulted in poor utilization. Every community or urban General Hospital cannot support a cardiopulmonary laboratory or afford the expensive construction and equipment required for a radiotherapy center. The study on "Prepayment for Hospital Care in New York State,"[5] known as "The Trussell Report," stresses this point. Unfortunately, the desire for prestige on the part of hospital boards and medical staffs has contributed to this problem. Secondly, there is a need for an open staff policy for qualified professional personnel at hospitals which have developed specialized facilities. This is a nationwide requirement and should be supported by organized medicine. Without this arrangement in a given area, medical talent cannot be fully utilized and the patient may not receive the best of professional care.

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* Presented at the Forty-sixth Annual Meeting of the American Radium Society, White Sulphur Springs, West Virginia, April 13-16, 1964.

Inasmuch as radiotherapy centers play so large a part in the management of cancer, either as separate entities or within cancer centers, and are expensive to develop, it is necessary to arrive at a clear understanding of how they may best serve the cancer patient population. In this connection, I have abstracted several of the recommendations of the British Ministry of Health's circular on the "Organisation of Radiotherapy Services for the Treatment of Cancer"[1] which are pertinent to the problem which I have raised:

1. Radiotherapy of cancer should be under the control of radiotherapists engaged solely in that work.

2. The radiotherapy center should be a department of a large hospital.

3. Megavoltage therapy is essential for the treatment of cancer and every center should have at least one piece of apparatus working in excess of 2 mev. peak with equivalent gamma-ray emission and working at a source axis distance of at least 75 cm. and a source skin distance of 60 cm. as the absolute minimum.

4. Regional centers should be linked with a University in the region and have a full range of equipment, a physics service, research facilities, adequate accommodations for patients, and a full consultant and ancillary staff.

5. Associated Treatment Centers should be established and their site and number should depend on the size and distribution of the population and the ease or difficulty of travel within the region. Since every treatment center should be equipped with megavoltage apparatus, the minimum staff must be two radiotherapists and one physicist. The area served by the center should provide a minimum of 600 new patients a year with malignant disease. One man centers treating fewer patients cannot be justified any longer.

6. Peripheral clinics are required for preliminary diagnosis, consultation on treatment, and follow-up examinations. It is here that the consulting radiotherapist may discuss the case with the appropriate specialist and general practitioner.

7. Radiotherapy beds should be provided in adequate numbers. Where a shortage exists, radiotherapists have been forced to undesirable curtailing of the total time of treatment, to treating as out-patients cases which should be admitted and to restricting the amount of palliative treatment carried out. Some even are compelled to have a waiting list of potentially curable cases.

With some modifications to suit our more complex situation due to the differences in population and geography, most of these recommendations could be widely adopted in this country.

One of the finest examples of cooperative municipal effort is the Radiation Center of Fort Worth, Texas.[6] This is a community facility established and operated by a non-profit organization. Its primary purpose is to treat cancer and allied diseases with supervoltage radiation. It does not duplicate or compete with any other institution in the area and represents the most economical means of providing expensive radiation therapy equipment and specialized personnel. It is one of the few open staff radiation facilities in this country and has been in operation since 1958. The center's charges are established only to cover its operational costs of treating the patient who pays such fees. No patient is ever denied treatment on account of his financial status. The charges are separate from and unrelated to any physician's professional fees which are arranged between the patient and the radiotherapist in the same manner as the surgeon would determine his fee for a surgical procedure.

Although I have presented some thoughts on the development of cancer centers in urban areas, particularly for radiotherapy, I have no intention of overlooking the patient who resides in the small community or rural area. The small community hospital may associate itself with an urban cancer facility and serve as a cancer detection center. Follow-up clinics by specialists from the urban center together with members of the local staff may be arranged. When the diagnosis of cancer has been established in a patient whose disease requires specialized treatment at a cancer center, he should be forwarded without delay. I have been advised by many of my colleagues that the average American is too independent for such a program and will refuse to leave his home area for treatment. Of this I am not convinced inasmuch as our population is well educated in the benefits of specialized medical services and equipment for the treatment of cancer. Only a rare and eccentric individual would refuse to leave his home area when advised that he has a much better chance of cure in a center than in his community hospital and no conscionable physician would disagree with this concept. Furthermore, it is common practice for a patient residing in our mid-western states to travel many miles from his home in order that he may receive treatment in one of the excellent University Centers. In one of our large metropolitan areas, the Green Point City Hospital in Brooklyn is operated by the Mount Sinai Hospital in New York City, 15 miles away. Patients requiring radiotherapy are referred to the Radiotherapy Center at Mount Sinai Hospital where they are hospitalized until their therapy has been completed. The patients cooperate extremely well and I can attest that they are deeply grateful for the care rendered them.

As a result of an extensive period of observation of the management of the patient with cancer and in keeping with his best interests, I am convinced that all such patients, private as well as ward or clinic patients, whose disease may be controlled by more than one modality of therapy should be examined by a qualified Tumor Board to determine the most suitable form of treatment. I have good reason to believe that, on occasions, economic factors dictate the type of therapy which the patient receives and this may not be in keeping with the best principles of cancer management. Paterson has clearly summarized the problem as follows: "When a patient with malignant disease presents himself or herself for treatment, certain broad initial decisions must be taken. In the first place, it must be decided whether the state of affairs is such that any form of treatment will be of sufficient value to justify the procedure. If the decision is in favour of treatment, it must then be determined whether it shall be by surgery, radiotherapy, or chemotherapy, or whether a combination of methods is indicated. Lastly, if the choice falls on radiotherapy, it is further necessary to make a clear decision between curative and palliative intention, a decision which must be made at the outset and which requires a critical review of all the circumstances of the case. This is essential since in practice curative therapy often necessitates prolonged treatment to a dosage near to the limits of tolerance for the volumes involved and entails considerable reaction of the normal tissues."

Although our medical personnel has reached a high degree of competence in the treatment of cancer, I am impressed that there are a few areas of endeavor which could be improved by more realistic requirements on the part of their respective specialty boards. I refer specifically to the training required for certification in otolaryngology, obstetrics and gynecology, and radiology. To the best of my knowledge, these are the only specialties wherein an individual who has passed the required examination may, on the basis of not more than one year of training in cancer management (and sometimes less), qualify and practice as a specialist in his respective field.

Inasmuch as radiotherapy is playing an increasing role in cancer management, it is most important that we make every effort to encourage more individuals to enter this specialty. However, it seems doubtful to me that any significant progress will be made in this area until more of our teaching centers recognize the necessity of dividing the field of general radiology into its component branches of diagnostic roentgenology and therapeutic radiology and offering separate training programs in each field under separate directors. Hopefully, when this era comes about, the Radiotherapeutic Professor will be allocated equal teaching time with the Diagnostic Professor for it is in the clinical years of medical school that the aspiring physician is, to a large degree, influenced in the selection of his ultimate endeavor. Kaplan[3] has succinctly phrased the outcome of continuing our present system when he states that "Treatment of small numbers of cancer patients by each of many hundreds of general radiologists has the two disadvantages of depriving some patients of, at least, a small fraction of whatever chance for cure they might otherwise have had and of making it difficult or impossible for the larger centers to accumulate enough case material in any one category to provide early and decisive answers to a host of clinical questions."

Nevertheless, the Nation will require the services of the general radiologist for many years to come and certainly until the transition period has been completed. Not only does he represent one of the most important cogs in the cancer detection team, but a large segment of the cancer population must be referred to him for palliative therapy in which endeavor he should be skilled. However, I would hope that his preceptors will inculcate him with the philosophy that, whenever possible, the patient with radiocurable cancer should be referred to a radiotherapist who has megavoltage equipment at his disposal.

Finally, all of us concerned with cancer management should make every effort, through the appropriate committee of our County Medical Societies, to persuade health insurance carriers to provide more adequate coverage for radiotherapy of cancer.

Radiotherapy Center
Mount Sinai Hospital
New York 29, New York

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Vol. 93, No. 1

TREATMENT OF EPITHELIOMA OF THE LATERAL OROPHARYNX WITH LOW INTENSITY RADIUM NEEDLE IMPLANTS*

By CHARLES L. MARTIN, M.D., *and* JAMES A. MARTIN, M.D.
DALLAS, TEXAS

STANDARD division of the human pharynx into three levels defined by clean horizontal planes has numerous obvious medical advantages. When, however, one wishes to perform a practical evaluation of pharyngeal neoplasms, the anatomical divisions become arbitrary. Use of the term "carcinoma of the oropharynx" usually becomes an attempt to standardize by anatomy that which is difficult to standardize because of numerous variations in histology and pathologic physiology. At the outset then, the term designates a heterogeneous mixture of entities and there is some delusion in reaching conclusions of presumed mathematical purity when the initial premise itself is poorly defined. Carcinoma of the tonsil, for example, often is carcinoma of the tonsil with its potentials intact only as long as it is confined within its fossa. Before detection, it may, by virtue of local extension, also become carcinoma of the palate, tonsillar pillars and tongue, complete with all the latent possibilities added by the extensions. To place this lesion exclusively in a study of cancer of the tonsil is no longer any more accurate than to claim it in a study of the tongue alone. To make pure prognostications upon a group that might be contaminated by salivary gland carcinoma of the lateral palate, lymphosarcoma of the tonsil and squamous cell carcinoma of the free epiglottic surface is akin to equating saints to sinners because they live in a common community.

The study presented here is designed as a report of a clinical experience with neoplasms in an area of the oropharynx simplified as much as possible by excluding as many variables as is feasible. Over a period of years, all cases of carcinoma arising in or involving structures of the lateral oropharynx have been studied. These are defined as lesions of: (1) the lateral soft palate, (2) the lateral pharyngeal wall, (3) both pillars, (4) the tonsil and tonsillar fossa, (5) the glossopharyngeal fold, and (6) the posterior gum, floor of mouth and adjacent portion of the tongue. The fact that approximately 140 tumors of this region have been seen clinically over a period of 35 years helps justify it as a category. In the interest of simplicity, study has been limited to an 8 year period in which all patients were treated with a single standardized radiation approach directed by no more than two operators working together. Only epithelial carcinoma has been considered since inclusion of other histological types introduces other variants (lymphosarcoma, lymphoepithelioma, adenocarcinoma, mixed tumors, etc.). With such refinement, the study is reduced to consideration of 67 consecutive patients, all of whom were treated 3 to 10 years ago. Conclusions are based on observation rather than prediction. Salvage is defined as "cured" or "alive and clinically free of cancer as judged by clinical examination." Interpretations are made in terms designed to respect the dual facts that the group is statistically small and not all biophysical variables can be standardized.

Within the limits defined, epithelial carcinoma of the lateral oropharynx exhibits some features common enough for comment. Occurrence is commonest in the male in his seventh decade, who will often admit a significant alcoholic intake, current or remote. Pain in the throat or ear, although the usual first complaint, is on occasion preceded by the appearance of cervical lymph node metastases. Local extension of the primary tumor to adjacent pharyngeal structures occurs often and, at times, follows a predictable pattern. Consider, for example, that carcinoma arising in the lower half of the anterior pillar favors migration medially across the posterior sulcus and into the adjacent tongue with enough frequency to dictate anticipation by the therapist. Lymphatic drainage is abundant and it is not surprising that lymph node extension from the area is reported in frequencies ranging from 2 to 4 out of 5 patients.[15] Distant hematogenous dissemination occurs relatively late but is significant in relation to common causes of the terminal event.

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* Presented at the Forty-sixth Annual Meeting of the American Radium Society, White Sulphur Springs, West Virginia, April 13-16, 1964.

TECHNIQUE

All primary lesions in this study were examined histologically and included only if designated as squamous cell carcinoma or transitional cell carcinoma, but only one transitional cell lesion was observed. Attempts to verify all metastatic cervical lesions were also made, usually by needle aspiration but, occasionally (and less desirably), by cold knife incision or excision prior to our initial patient contact. Otherwise, the lymph node masses were determined clinically as metastatic when they were firm, nontender, persistent, 1 or more centimeters in diameter and appeared in conjunction with a known primary lesion.

The therapeutic approach in all patients has been the use of interstitial low intensity radium needles both to the primary lesion and its cervical metastases as described in detail elsewhere.[10] Orthovoltage roentgen therapy has been added to the neck directly over the radium implant within the lymph nodes, but no roentgen therapy has been given in the absence of palpable lymph nodes.[8,9] Most of the tumors lend themselves well to the principle of layer or single plane implants. Occasionally, the implantation of a large mass is not easy and the establishment of a good pattern requires some experience tempered by patience and attention to detail. In general, the larger the primary lesion and hence the more extensive and complex the applied needle pattern, the more chance there will be for "hot spots" and resultant necroses. It follows from reason and experience that one's zeal to be adequate in treating small lesions can result in the antithesis which is overtreatment and damage.

Needle patterns are designed to approximate cancerocidal dosage to the extent of palpable tumor and conform (within anatomical limitations) to planar schemes known to deliver a satisfactory dosage range in approximately 168 hours (1 week). Roentgen-ray dosage, when added over cervical lymph node implants, is recorded separately. At the moment, we prefer this rather elongated dosage expression to the use of a single dosage figure at an arbitrary depth and have not converted to the use of rads. We are aware that this is antiquity, but also that dosages are not uniform, some tissue absorption occurs in or close to bone and the nominal mixture of two radiant energies as one is difficult to reconcile in terms of biological response. When a lesion and its metastases are treated concurrently, meticulous care to avoid overlapping and "crossfiring" of mandibular bone has been rewarded by the elimination of any significant osteonecrosis. Illustrative cases with patterns of the technique used are presented in Figure 1 through Figure 6.

In the event of tumor recurrence or tissue necrosis, the importance of aid from a well trained surgeon cannot be overemphasized. He must be able to recognize and resect all damaged soft tissue and bone but very radical procedures such as mandibulectomies are seldom found necessary. Even in the well advanced cases, he can often improve the patient's well being for long periods, thereby augmenting the value of our therapy.

CLINICAL RESULTS

Currently, there is an intellectual accept-

Table I

OUTCOME IN 17 PATIENTS WITH EPITHELIOMA IN LATERAL OROPHARYNX TREATED WITH RADIUM NEEDLES 3 TO 4 YEARS AGO

Healing of primary lesion in 2 to 3 months		16 of 17—90.5%
Alive at 3 years with no evidence of cancer		9 of 17—55.0%
Known dead of cancer at 3 years		5 of 17—29.4%
Dead of intercurrent disease—No cancer at last visit	2	
Untraced	1	
Indeterminate group	3	
Alive 3 years—determinate group		9 of 14—64.2%

ance of methods of tabulating treatment survival rates as mathematical extrapolations from limited clinical observations into terms of "5 year survivals;" useful for the reason that 2 and 3 year experiences may be employed to increase the "confidence limits" at 5 years, and presumably reduce the temporal tedium once considered necessary. Without wishing to be overly critical of this system, the authors feel that there are many among us who perhaps are not mathematically enlightened to the point of its full appreciation. The idea that 2 and 3 year observations can be valid is one that must be defined with much clarity. Consider, for example, the information tabulated in Table I which recounts experience with a statistically minute and carefully selected group of patients treated 3 and 4 years previously. The "cure rate" at 3 years is a most satisfying 55 per cent which can be garnished by excluding the unclean factor "indeterminate," thus producing an appealing 64 per cent. This is a factual presentation of a real 3 year experience including all of the patients treated, but it is obviously meaningless as it stands. There are also, to be sure, limitations to the validity of straight reporting of witnessed events. Nevertheless, this method enjoys the virtue of simplicity and, carefully done, it remains scientifically sound; thus, it competes with the computer.

During the period of 8 years including 1953 through 1960, a total of 67 consecutive epitheliomas of the lateral oropharynx was admitted for treatment, 50 of which qualify for 5 year evaluations. Let us emphasize the fact that the figure 67 represents all of the epitheliomas of the lateral oropharynx during the 8 years specified above. Rapid regression and healing was observed in 85 per cent to 90 per cent of the primary epitheliomas within 2 to 3 months after treatment. Of the total group (Table II), 21 were alive at the end of 5 years, a "survival rate" of 42 per cent. This closely matches the 43 per cent reported by Scanlon *et al.*[13] of the

Table II

FIFTY CASES OF EPITHELIOMA PRIMARY IN LATERAL OROPHARYNX TREATED WITH RADIUM NEEDLES 5 TO 10 YEARS AGO

Healing of primary lesion in 2 to 3 months in 43 cases		86.0%
Alive with no cancer found at 5 years		16 of 50—32.0%
5 year survival		21 of 50—42.0%
Dead of intercurrent disease—No cancer reported	4	
Untraced—No cancer at last visit	3	
Indeterminate group	7	
Alive 5 years with no cancer—determinate group		16 of 43—37.2%
5 year survival—determinate group		21 of 43—50.0%

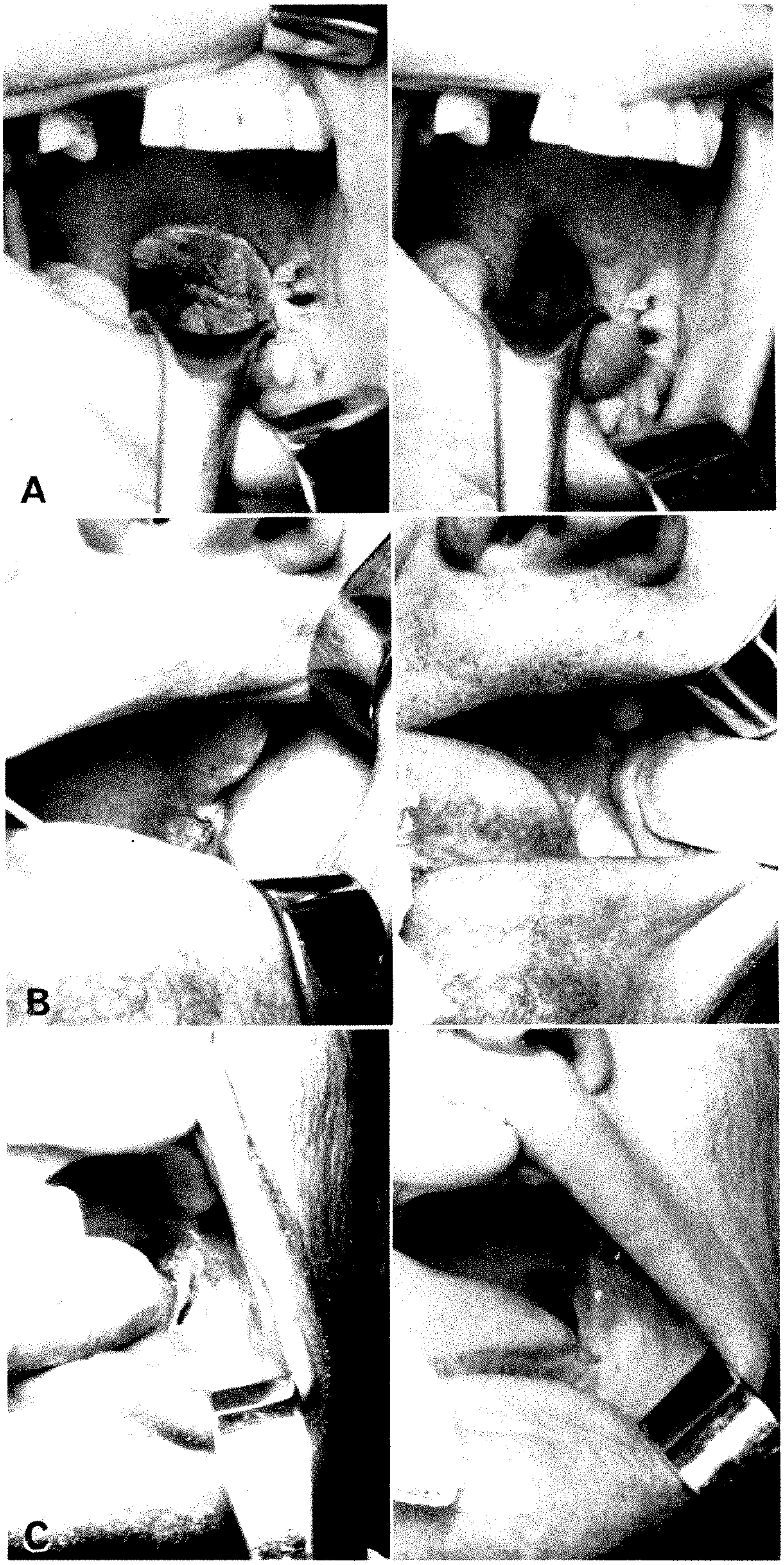
A
B
C

TABLE III

FOLLOW-UP OF 16 PATIENTS WITH EPITHELIOMA OF LATERAL OROPHARYNX SHOWING NO CANCER AT 5 YEARS

Well 5 years	6	Well 7 years	2	Well 9 years	1
Well 6 years	4	Well 8 years	2	Well 10 years	1

Mayo Clinic for treatment of cancer of the palatine tonsil. However, a careful examination of our 21 "surviving" patients revealed cancer still present in 5 so that our actual 5 year cure rate was 16 of 50 patients or 32.0 per cent. The Mayo group reported 46 patients of whom only 31 had squamous or transitional cell cancers and their 5 year survival rate in this group amounted to 10 or only 33 per cent, which approximates our cure rate for the same types of cancer. We mention this article because the material (regardless of the title) and the results are similar to our own. It also illustrates the numerous variables encountered in published articles since treatment alone consisted of combinations of surgery, electrocoagulation, external irradiation and interstitial irradiation.

The negative follow-up examinations of our 16 cases found cancer free at 5 years (Table III), indicating that the cancer has not recurred in periods varying from 5 to 10 years, forms our chief argument for the continued use of the term "5 year cure rate." The fatal outcomes observed in the 5 cases in which cancer was still present at 5 years (Table IV) constitutes our strongest argument against the use of the term "5 year survival" as an indication of ultimate prognosis.

There are, therefore, 34 cases known to be dead or untraced. In 11 the role played by cancer could not be determined. Three were lost to follow-up while in good condition, 4 died of intercurrent disease and the cause of death could not be accurately ascertained in 4 others (Table V). This leaves 23 cases reported as dead of cancer (Table VI). Only the most significant facts are listed in this table. The first item covering 6 patients that have not returned for examination or further treatment is a source of annoyance. Such cases usually live in far

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FIG. 1. (*A*) Squamous cell carcinoma (Grade II) involving left soft palate and anterior pillar. Low intensity radium needle implantation done on May 29, 1956. Deep seated lymph node under anterior edge of upper sternomastoid muscle implanted 6 months later; 6×350 r in air (260 kv.) given daily to 10×10 cm. area centered over lymph nodes with radium in place. Biopsies of suspicious areas in left pyriform sinus and neck negative at 4 years. Patient free of demonstrable cancer at 7 years. Photograph on right, made 6 weeks after first radium implantation, shows complete healing. (*B*) Squamous cell carcinoma (Grade III) involving left upper anterior pillar and soft palate implanted on May 22, 1956 in patient with severe bilateral pulmonary emphysema and fibrosis. Complete healing at 6 weeks shown in photograph on right. No lymph node involvement at any time. Autopsy following death from pulmonary disease at $6\frac{1}{2}$ years showed no evidence of cancer. (*C*) Squamous cell carcinoma (medium grade) involving all of the left anterior pillar and extending across the floor of the mouth into the posterior lateral tongue. No lymph node involvement at any time. Radium implantation of anterior pillar and tongue done on June 12, 1953. Photograph on right shows almost complete healing at 6 weeks. Local necrosis at 6 months cured with gentian violet in Scott's solution. Patient free of demonstrable cancer and working every day at 10 years.

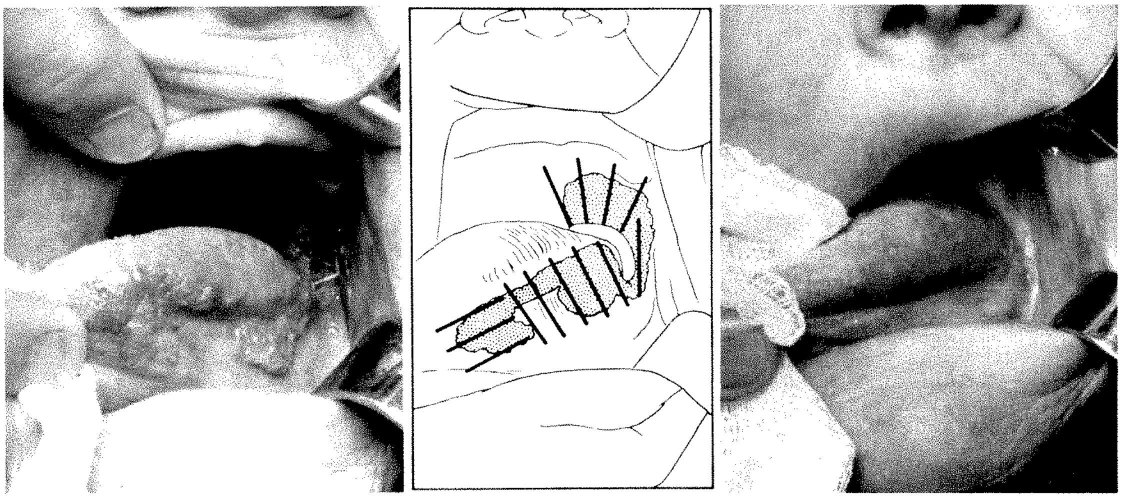

FIG. 2. Squamous cell carcinoma (Grade III) involving the left soft palate, anterior pillar, posterior floor of mouth and posterior two-thirds of lateral border of the tongue before and 5 months after the implant indicated in the diagram. No cervical lymph node involvement found at any time. She felt well and showed no evidence of cancer at the end of 5 years and 1 month.

TABLE IV

OUTCOME OF 5 PATIENTS ALIVE WITH CANCER AT 5 YEARS

1. Primary lesion well. Treatment of recurrence refused. Died at 5 years, 1 week
2. Primary lesion well. Treatment of new cancer in cheek refused. Died at 5½ years
3. Primary lesion well. Metastatic cervical lymph nodes treated elsewhere. Died at 6 years
4. Primary lesion well. Metastatic cervical lymph nodes treated elsewhere. Died at 7½ years
5. Primary lesion well. Extension into ear treated elsewhere. Died at 8 years, 2 months

TABLE V

OUTCOME OF 34 OF 50 CASES NOT KNOWN TO BE CURED OF CANCER

Untraced. No death certificate in State Bureau of Vital Statistics	3
Dead of intercurrent disease. No cancer at last visit	4
Dead of unknown cause	4
	11
Reported dead of cancer—34 minus 11	23

TABLE VI

PROGRESS OF 23 CASES REPORTED TO BE DEAD OF CANCER TREATED 5 TO 10 YEARS AGO

Did not return for examination or more treatment	6
Dead of pulmonary cancer—roentgenographic diagnosis	6
Dead of large recurrences	7
Dead of tongue hemorrhage after excessive roentgen therapy given elsewhere	1
Dead of late recurrence in inner ear (8 years)	1
Dead of brain metastases (4 years)	1
Dead of metastases in low cervical lymph nodes (7 years) treated elsewhere	1
	23

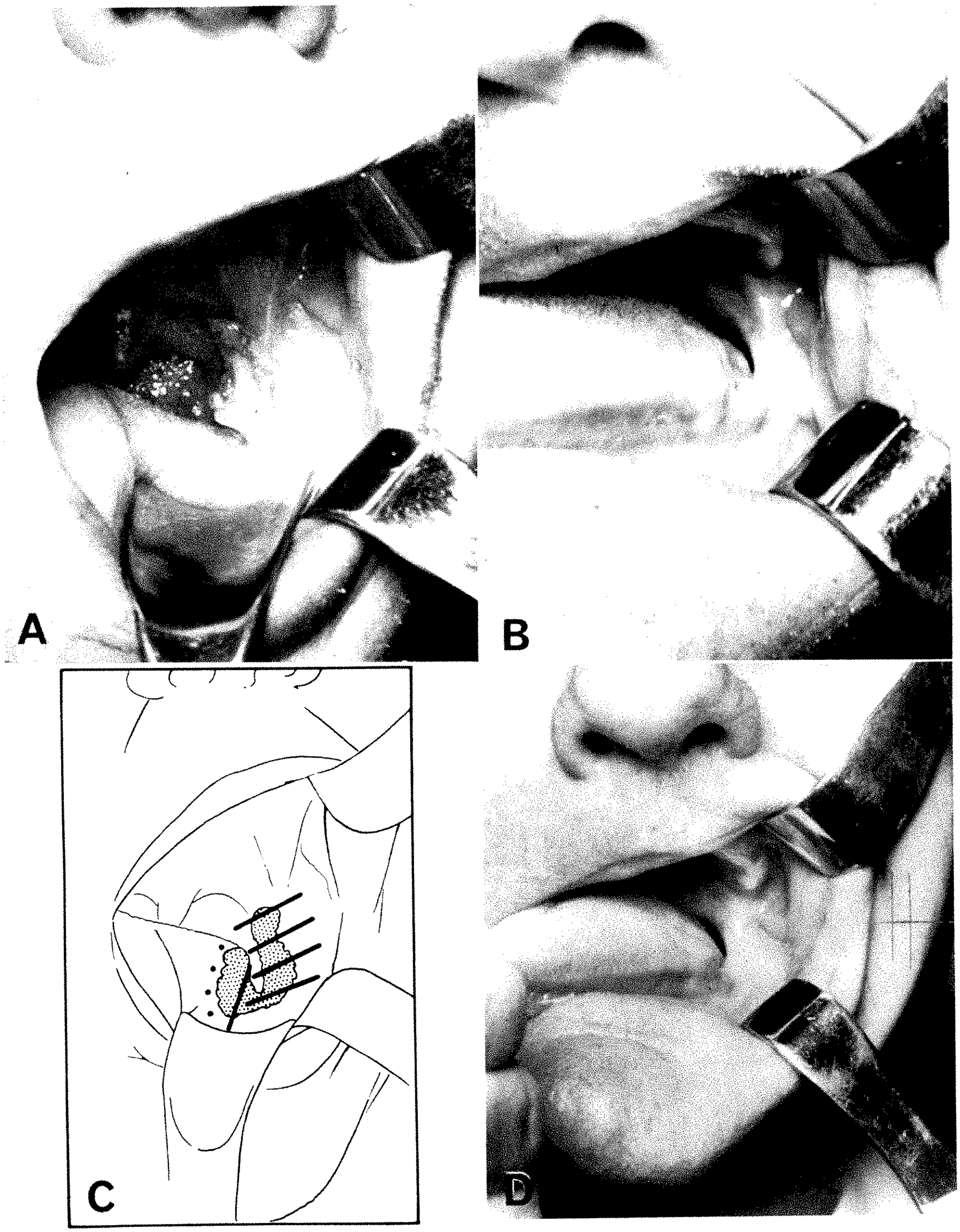

Fig. 3. (*A*) Squamous cell carcinoma of the left anterior pillar extending into tonsillar fossa implanted with 4 low intensity radium needles. (*B*) New growth in floor of mouth and lateral posterior tongue below smooth scar at original treatment site implanted at 10 months with 5 low intensity cobalt 60 needles. (*C*) Both implants indicated in a single diagram. (*D*) Treated areas smoothly healed. Patient died elsewhere at 7½ years after receiving roentgen therapy for a pulmonary lesion (? Pancoast tumor) and enlarged cervical lymph nodes. Mouth still well.

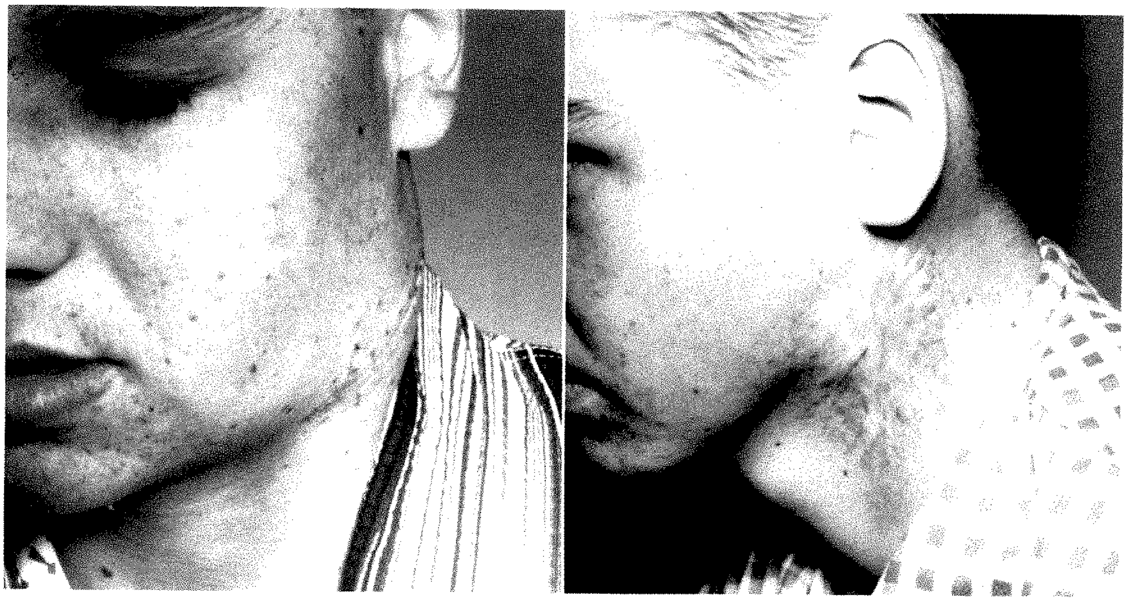

FIG. 4. A boy, 17 years of age, before and 11 months after low intensity radium needle implantations of post-operative recurrences of transitional cell carcinoma in the left tonsil and upper cervical lymph nodes. The latter received our usual orthovoltage roentgen therapy. At 7 years, 4 months a flat squamous cell carcinoma (new lesion) growing beneath the neck scar was resected and the defect covered with a graft. He feels well and is free of any evidence of cancer at 9 years.

distant sparsely populated districts where visits to the local physician are so inconvenient that they are reserved for emergencies only. Neither the doctor nor the patient answers letters and news of the fatal outcome is reported by a friend or a relative who knows no details. Death certificates often give causes of death flavored by the knowledge that treatment was once given for cancer and there our quest for information ends. It seems possible that a few cures could have been achieved in this group, but with no data available no conclusions can be made.

The 16 deaths from incurable metastases and recurrences are obvious failures but the patient that died from a ruptured lingual artery in a portion of the tongue over-treated with external roentgen rays might have been salvaged if the primary lesion had been properly handled at an earlier date.

The good apparent cure rate of 55 per cent in our cases with cervical lymph node metastases followed for 3 years (Table VII) which drops to 24 per cent at 5 years illustrates the treacherous nature of this complication. It is significant that none of the patients with contralateral or bilateral cervical extension was among the 5 year survivors. In spite of this over-all figure, there are some patients in the group who came in because of large fixed masses of lymph nodes in the neck secondary to small carcinomas in the lateral oropharynx and in whom excellent results lasting 7 to 11

TABLE VII

PATIENTS WITH CANCER OF LATERAL OROPHARYNX HAVING METASTATIC CERVICAL LYMPH NODES

Treated 3 to 4 years ago	9 to 17—50.0%
No palpable lymph nodes at 3 years	5 of 9—55.0%
Treated 5 to 10 years ago	25 of 50—50.0%
No palpable lymph nodes at 5 years	6 of 25—24.0%

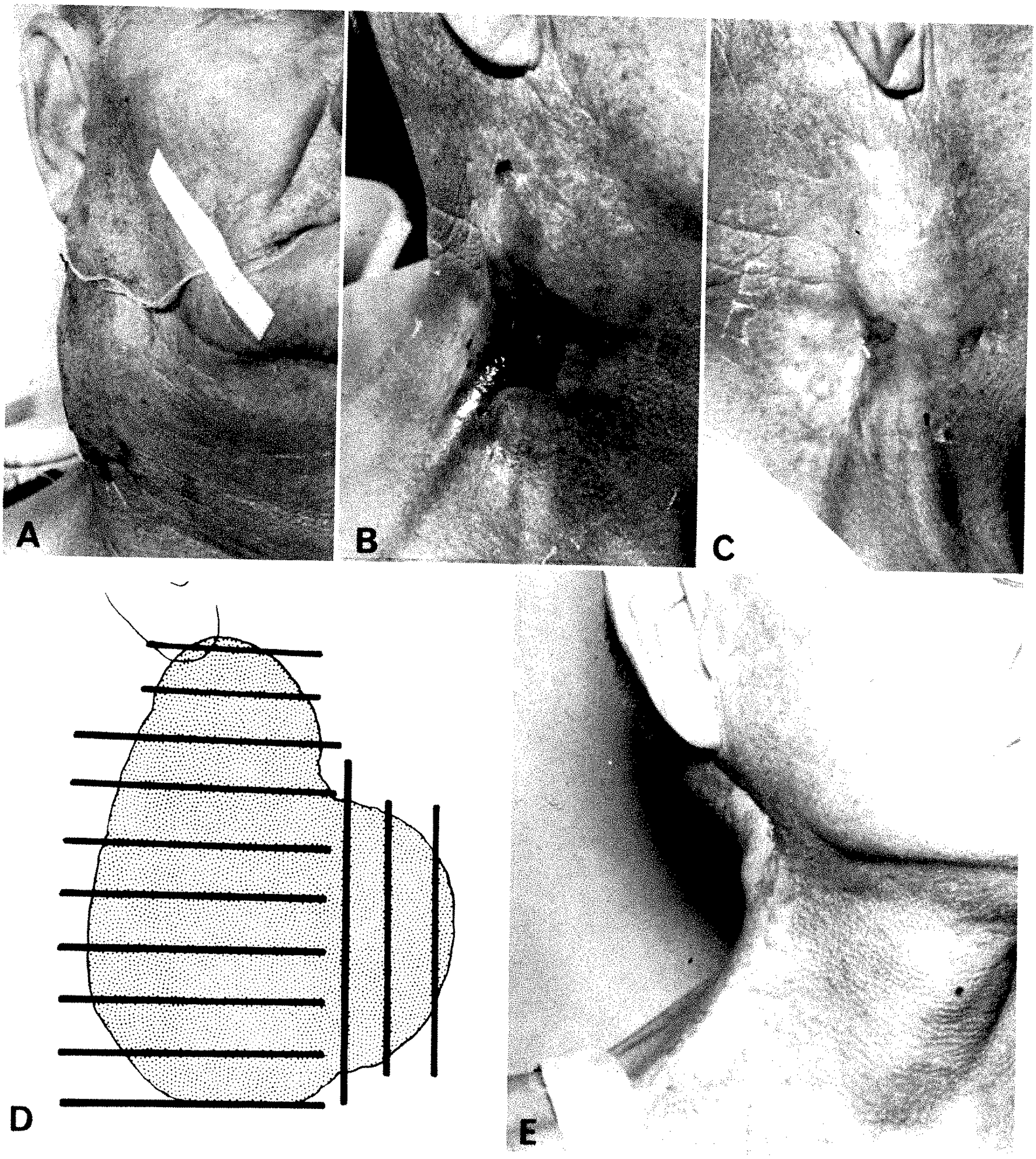

Fig. 5. (*A*) Photograph made after low intensity radium needle implantations of squamous cell carcinoma Grade III of right tonsil and large fixed metastatic cervical mass in right neck. Orthovoltage roentgen therapy was given to cervical tumor while radium was in place, with careful shielding of lower jaw and oropharynx. (*B*) Denudation of skin of neck with marked regression of both tumors at 6 weeks. (*C*) Elongated dense scar about sternomastoid muscle with central painful necrotic area resected and defect covered by a graft with gradual relief of pain at 1 year. (*D*) Original extensive layer implant beneath cervical mass. (*E*) At 6 years he felt well except for some intermittent discomfort in the neck and lower esophagus. At $13\frac{1}{2}$ years he shows no evidence of cancer and is receiving dilatation for a benign stricture of the lower esophagus.

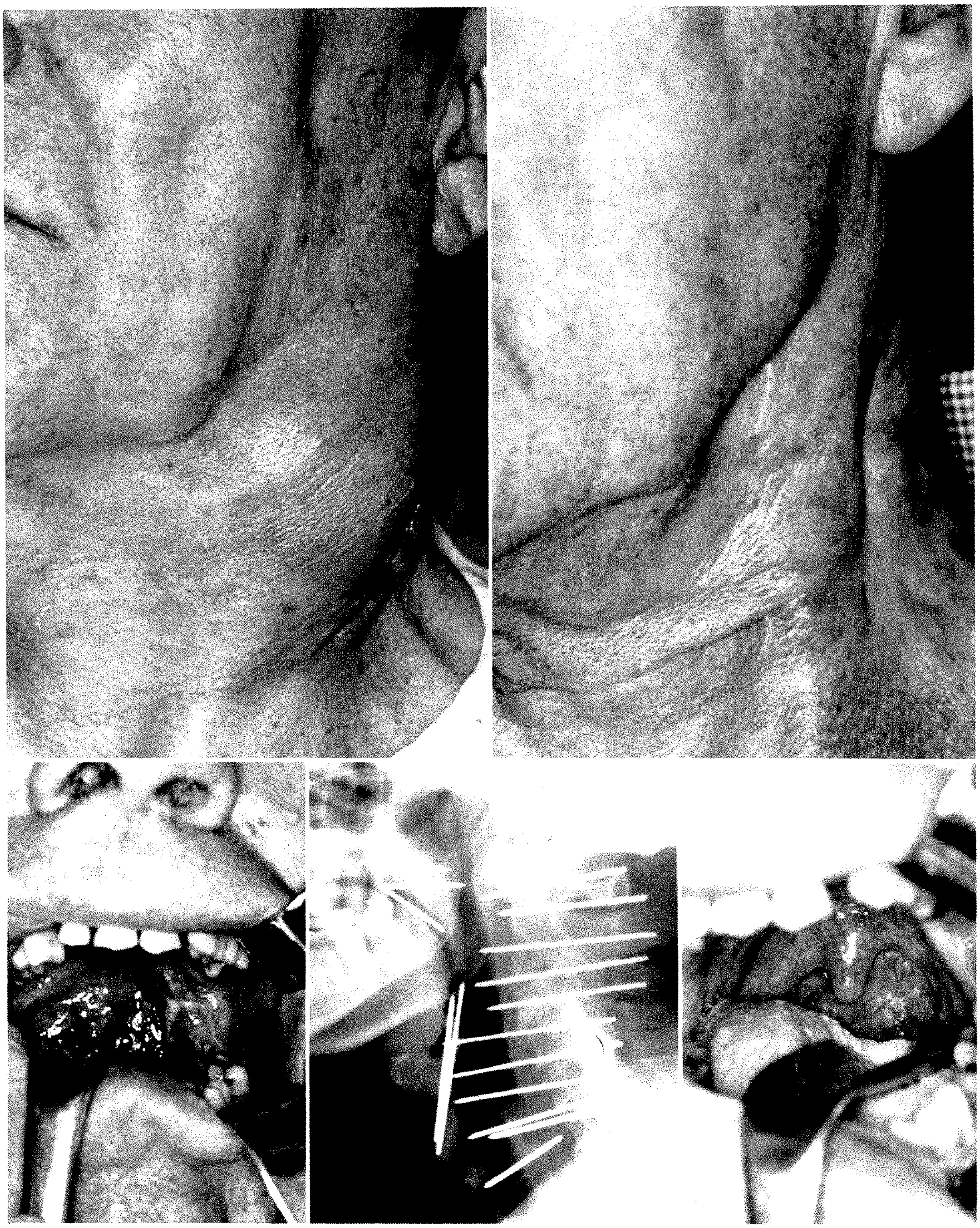

FIG. 6. Photographs made before and 5 months after our routine radium needle and roentgen-ray technique for a squamous cell carcinoma of the left anterior pillar and soft palate and a large fixed residual mass of metastatic cervical lymph nodes recently subjected to surgery. At 4 years no evidence of cancer is found in the mouth or neck but he has some hoarseness and intermittent difficulty in swallowing produced by a concentrated needle pattern over the left side of the larynx.

TABLE VIII

SIX ADVANCED CASES OPERATED ON AFTER IRRADIATION FAILURE

1. Primary healed. Radical neck dissection at 4 months. Died of pulmonary metastases—1 year, 3 months
2. Local necrosis resected. Bilateral lymph node involvement. Died of pulmonary metastases—4 years
3. Primary lesion healed. Bilateral lymph nodes resected. Died of local recurrence—2 years, 3 months
4. Local radiation ulcer resected. Died of cirrhosis of liver—13 months
5. Two resections of local recurrence. Died elsewhere, unknown cause—2 years
6. Primary lesion healed. Radical neck dissection at 3 years. Died of pulmonary metastases—4 years

or more years were obtained. In our experience radical surgical procedures have not done so well with such lesions.

Although we expect no miracles from surgery performed on advanced irradiation failures, we still refer such patients to a competent surgeon because he can often give them real relief of discomfort. The ultimate outcomes observed in such cases are tabulated in Table VIII, which illustrates the complications that usually render a cure impossible. The type of postirradiation cases in which surgery has converted failures into cures and has completely relieved the pain occasionally produced in residual scars is included in Table IX.

DISCUSSION

It is difficult to compare experiences when one wishes to speak of carcinoma of the oropharynx. In general, the current tendency in radiation therapy is to categorize a group of dissimilar primary neoplasms as alike because they are so defined anatomically.[1] Many centers advocate external irradiation as the prime treatment approach, often to the cervical area of established or potential spread as well as to the primary lesion, and occasionally augmented by interstitial therapy. Many apparently feel that the "super-energy" devices produce better clinical results while a considerable portion of the published data relates orthovoltage experience.[5] Evaluation of clinical data is complex, especially when numerous techniques are reported as one vast experience,[14] and when clinical results are elaborated biometrically in terms of survivals (rather than cures), determinate and age adjusted factors and with mathematical predictions projected beyond experience.[7] The value of a pure clinical experience simply evaluated from a clinical view should be complementary.

The treatment method outlined in this report has advantages worthy of mention. Fundamentally, the principle of approximation of low intensity interstitial sources to the disease only obviates radiation exposure to large normal tissue volumes otherwise necessitated by external treatment fields. The radium scar is little larger than the size of the tumor it replaced and soft tissue atrophy and fibrosis of large areas in the pharynx are avoided, particularly when the primary tumor is small.

It is generally known that patients in the group under discussion may, on occasions, experience a second neoplasm in the oral or pharyngeal mucosa even years after the first has healed. Regardless of whether this is labeled as a recurrence or a new primary lesion, published experience would suggest that large treatment fields applied to wide mucosal areas fail to obviate this unfortunate occurrence, but do effectively com-

TABLE IX

POSTIRRADIATION SURGERY IN 4 OF 18 CASES FREE OF CANCER AND TREATED 5 TO 10 YEARS AGO

1. New cancer in large neck scar resected at 7 years, 9 months. Well at 9 years
2. Painful benign scars in mouth resected in 2 patients. Well 6 and 7 years
3. Small recurrence in treated pharynx resected. Well 8 years

promise hope for subsequent radiation success. The limited radiation produced by the interstitial method often makes it possible to reapply treatment to closely adjacent areas without serious fear of tissue disaster. Limitation of this nature also minimizes the effect upon the salivary glands. Early parotid swelling and late "chronic dry mouth" are eliminated, appetite recurs in a reasonable time and the delay and discomfort of preliminary full mouth extractions of sound teeth are not necessary. The principles and mechanics of radium needle insertions are simple, particularly in the face of some of the surgical procedures common about the head and neck. Radiation exposure to the operator's hands occurs but apparently without the dire consequences witnessed from the higher intensity sources of the past.[6]

Primary regression and healing of the pharyngeal lesions are the rule. The rate of residual or recurrent tumor is low and as soon as identified demands surgical help. Radiation necrosis when it occurs in soft tissue is usually in a limited area and its surgical correction is enhanced by the presence of healthy tissue free of fibrosis and edema in adjacent areas. Radiation bone damage is rare but also usually requires surgical excision. These complications generally occur within the first year of observation. The authors, however, have some anxieties regarding the possibilities of late complications when large fields about the neck and jaw are subjected to heavy external radiation doses in other clinics, and results are tabulated as mathematical projections beyond relatively short observations. Damage to nerve tissue in the cervical cord, for example, is a very real and serious complication which is inseparable from the subject and can be evaluated only by observation.[3,6]

Tumor therapy is designed ultimately to be lethal at the cellular level. It follows that damage of varying degrees will occur in normal tissue, some of which will defy normal efforts at repair. In theory at least, one should be able to apply progressive refinements in technique which would allow an approach to a complication rate of zero without sacrificing reasonable salvage. A tendency among some to excuse a given level of serious consequences as "acceptable" is, on the other hand, unrealistic.

For many years, we have adhered to the rule that more radiation must not be given to an area which has been adequately treated at a previous visit even though recurrences may be present. One of our most unpleasant problems consists of the care of a patient who has received 2, 3 or even 4 courses of radiation therapy elsewhere for a carcinoma of the pharynx and comes in with a large painful dirty slough within which tumor is still growing. Certainly, more irradiation is contraindicated and the surgeon's chances are severely limited. However, the good surgeon who is willing to clean up the damaged tissues and use antibiotics, blood transfusions, tube feeding and other supportive measures often can produce marked palliation, and occasionally will render such a patient operable.

SUMMARY

It has been conceded with obvious logic that a small clinical experience properly evaluated and carefully analyzed can be of considerable scientific value.[2] An effort is presented in which a generally complex subject has been reduced as much as possible toward uniformity. In 50 consecutively treated cases of epithelial carcinoma arising in the lateral oropharynx, 1 in 3 has been observed living without evidence of cancer at the end of 5 years, with a good chance of having no recurrences. This salvage compares well with results in other centers but unfortunately does not represent a striking modern advance in ability to cure.[4,5,12,16] As observed elsewhere, failure regardless of technique employed seems to remain largely dependent upon what point in time circumstances direct the patient toward therapy; that is, extent of the primary occurrence of lymphatic extension and the nature of prior treatment.

One, therefore, must consider the importance of other factors inseparable from the subject such as patient comfort, morbidity and frequency of sequelae and the facility and economics of the treatment method. With the low intensity interstitial method described, many of the discomforts inherent in external irradiation of all types are precluded. The method often provides considerable palliative value even when cure is not achieved. The rate of radiation sequelae is moderate, and the serious complications are largely excluded as are the chances of mortal consequence. The required therapeutic arsenal compares favorably with high energy machines, laminagraphic apparatus and complex computer systems primarily by virtue of its considerably smaller purchase price. Contrary to the opinion of some, the treatment method described is no more difficult in theory or application than any other interstitial approach. In the final analysis, it is felt that the primary axiom, perhaps too simple to be science, should dictate that therapy be directed toward making a patient better while striving for a cure rather than just a prolonged survival.

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THE PLACE OF RADIOTHERAPY IN THE TREATMENT OF TUMORS OF THE BASE OF THE TONGUE[*]

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IN THE years 1945–1962, 265 patients with tumors of the base of the tongue were seen at the Royal Marsden Hospital. Of these, 6 were not treated and 9 patients had recurrent disease (Table I). In this group are included not only those tumors affecting the posterior third of the tongue, but also those arising in the vallecula and linguo-tonsillar sulcus, since their natural history, treatment and prognosis are similar.

As with other tumors of the head and neck region, this is mainly a disease of the older patients, particularly those in the 60 to 80 year decades. In this group the youngest patient, aged 28 years, had a cylindroma of the linguo-tonsillar sulcus, and the oldest, aged 92 years, also had a tumor in this site (Table II).

The commonest symptoms were concerned with swallowing. In all 3 sites a sore throat or actual dysphagia, often caused by the bulk of the tumor, was the usual initial symptom. Definite pain, as compared with soreness, was noted especially in the linguo-tonsillar sulcus group. However, the most startling finding was the large number of patients in whom a lump in the neck was the first sign of disease (Table III). This was particularly common in cases with posterior third of tongue lesions, and means that virtually one-sixth of the patients have little chance of survival when first seen. The advanced nature of the disease in so many patients is surprising when one sees how quickly most of them come for treatment, well over one-half coming within 6 months of the time when symptoms first appear (Table IV). This may, of course, be a false conclusion, since many of these patients are old, and the onset of the disease may be so insidious that early signs are not noticed.

TABLE I

THE ROYAL MARSDEN HOSPITAL
TUMORS OF THE BASE OF TONGUE
1945–1962
TOTAL CASES 265

	Posterior One-third of Tongue	Vallecula	Linguo-Tonsillar Sulcus	Total
New Cases Treated	81	88	81	250
Recurrent Cases Treated	3	4	2	9
Cases Not Treated	2	—	4	6
Total	86	92	87	265

Unlike the anterior two-thirds of the tongue, where it is unusual to find tumors other than those of squamous cell origin, the base of the tongue gives rise to lesions of various histologic types. The most common is squamous cell carcinoma, but others include the anaplastic group—most frequent in the posterior one-third of the tongue and vallecula, and the sarcomas—most frequent in the posterior third of the tongue. Lymphosarcomas are found more often than reticulum cell sarcomas, in the proportion of 11 to 4. The salivary gland tumors belong to the so-called ectopic group and in our series were all malignant, 5 being cylindromata and 2 frank adenocarcinomata. In addition to the histologic type of the lesions, Table V also shows that

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[*] Presented at the Forty-fifth Annual Meeting of the American Radium Society, San Francisco, California, April 2–4, 1963.

TABLE II

THE ROYAL MARSDEN HOSPITAL
TUMORS OF THE BASE OF TONGUE
1945–1962
AGE INCIDENCE ACCORDING TO SITE
Previously Untreated Cases

Age	Posterior One-third of Tongue	Vallecula	Linguo-Tonsillar Sulcus	Total
20–30	—	—	1	1
30–40	1	—	2	3
40–50	4	4	6	14
50–60	11	12	19	42
60–70	33	31	19	83
70–80	27	34	28	89
80–90	5	7	5	17
90+	—	—	1	1
Total	81	88	81	250

TABLE IV

THE ROYAL MARSDEN HOSPITAL
TUMORS OF THE BASE OF TONGUE
1945–1962
DURATION OF SYMPTOMS ACCORDING TO SITE
Previously Untreated Cases

Duration	Posterior One-third of Tongue	Vallecula	Linguo-Tonsillar Sulcus	Total
Up to 3 mo.	41	38	29	108
Up to 6 mo.	20	24	28	72
Up to 9 mo.	7	13	8	28
Up to 1 yr.	9	6	11	26
Over 1 yr.	4	7	5	16
Total	81	88	81	250

disease in this site is predominantly one of men, only 24 women being affected compared with 226 men. This same proportion is generally found in malignant disease in the head and neck region.

There are many problems in treating malignant disease, not the least being the early appearance of metastases in lymph nodes. This is true in base of the tongue lesions (Table VI). If the squamous cell and anaplastic tumors are added together, then out of a total of 208 cases, only 49 patients had no lymph node metastases when first seen, and of these a certain proportion must have had malignant lymph nodes which were not detected by palpation. In spite of what one might anticipate, there is not a higher incidence of lymph node involvement in the anaplastic group. It is interesting to note that patients with linguo-tonsillar sulcus tumors have not only a high incidence of unilateral lymph node metastases, which is not unexpected in view of the ease with which the disease can escape to the neck from the throat, but that

TABLE III

THE ROYAL MARSDEN HOSPITAL
TUMORS OF THE BASE OF TONGUE
1945–1962
INITIAL SYMPTOMS ACCORDING TO SITE
Previously Untreated Cases

Site	Dysphagia	Sore Throat	Voice Change	Lump in Neck	Pain	Lump in Throat	Symptoms	Total
Posterior One-third of Tongue	10	24	4	21	9	3	10	81
Vallecula	25	24	5	11	10	2	11	88
Linguo-tonsillar Sulcus	11	23	1	11	19	4	12	81
Total	46	71	10	43	38	9	33	250

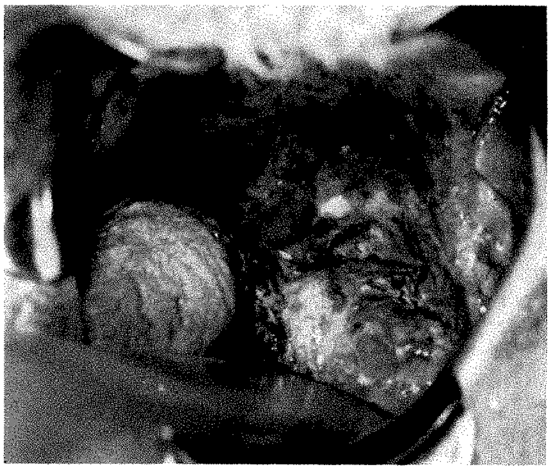

FIG. 1. Proliferative tumor in posterior one-third of the tongue.

so many of the patients in this group also have bilateral lymph node involvement.

DIAGNOSIS

The onset of this disease is often so insidious that the tumor is extensive by the time the patient seeks medical attention. Merely the use of a tongue depressor will often reveal a proliferative tumor arising from any of the three sites, particularly in the posterior one-third of the tongue (Fig. 1).

In the vallecula and the linguo-tonsillar sulcus, the lesion is more likely to be ulcerated, and the use of a laryngeal mirror is necessary. Occasionally, the base of the tongue lesion is ulcerative and infiltrative in character, burrowing forwards into the anterior part of the tongue and the floor of the mouth, causing edema of these tissues so great that examination of the oropharynx is virtually impossible. At the same time direct spread into the neck may cause diffuse fullness around the whole of the upper region (Fig. 2).

Soft tissue roentgenography is often a help in distinguishing the lower limits of these proliferative tumors, which may not be easily distinguishable on direct laryngoscopy (Fig. 3).

TREATMENT

As has been stated previously, most patients with lesions of the base of the tongue are elderly and with advanced disease when first seen. There is, therefore, more of a tendency for the surgeon to refer these pa-

TABLE V

THE ROYAL MARSDEN HOSPITAL
TUMORS OF THE BASE OF TONGUE
1945–1962
SITE AND HISTOLOGY

Previously Untreated Cases

Site	Squamous Cell	Anaplastic	Sarcomas	Salivary Gland Tumor	Negative or No Biopsy	Total
Posterior One-third of Tongue	49 (43M:6F)	12 (12M:0F)	9 (7M:2F)	5 (3M:2F)	6 (4M:2F)	81 (69M:12F)
Vallecula	65 (60M:5F)	16 (15M:1F)	3 (3M:0F)	—	4 (3M:1F)	88 (81M:7F)
Linguo-Tonsillar Sulcus	57 (56M:1F)	9 (8M:1F)	3 (2M:1F)	2 (2M:0F)	10 (8M:2F)	81 (76M:5F)
Total	171 (159M:12F)	37 (35M:2F)	15 (12M:3F)	7 (5M:2F)	20 (15M:5F)	250 (226M:24F)

tients for radiotherapy than those with disease in many other sites. In our series, a combination of radiotherapy and surgery, in that order, often proved to be the most beneficial. The type of radiation treatment varied according to the histology of the tumor.

RETICULOSES

Radiotherapy, occasionally aided by chemotherapy, has been the treatment of choice in the reticuloses. The tumor and the lymph nodes on both sides of the neck from the base of the skull to the clavicle were irradiated, usually at 250 kv. and a tumor does of between 3,500 r to 4,000 r, these being often the less sensitive types of the reticuloses. Most of these patients die from local disease, although general dissemination may occur.

SALIVARY GLAND TUMORS

Salivary gland tumors usually require a combination of radiotherapy and surgery. All the patients in this group had preliminary radiotherapy. Three patients (1 with linguo-tonsillar sulcus and 2 with posterior third of tongue tumors) were treated with radiotherapy only and have survived, but the others needed supplementary surgery. Unless the lymph nodes were initially palpable, only the tumor area was treated. These are comparatively radioresistant tumors and a high dose of radiation is necessary. A total tumor dose of 6,500 r to 7,000 r with telecobalt therapy or 2 mev. roentgen therapy was given.

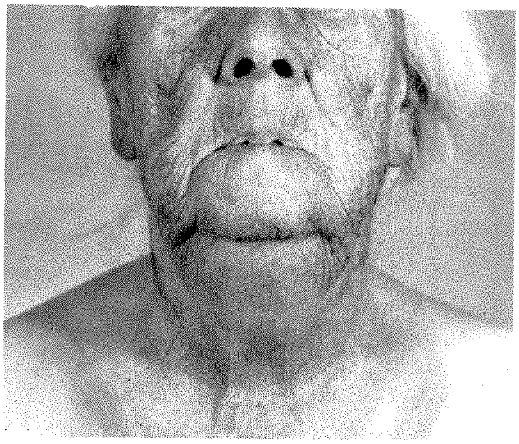

FIG. 2. Base of the tongue lesion with spread into the neck causing edema.

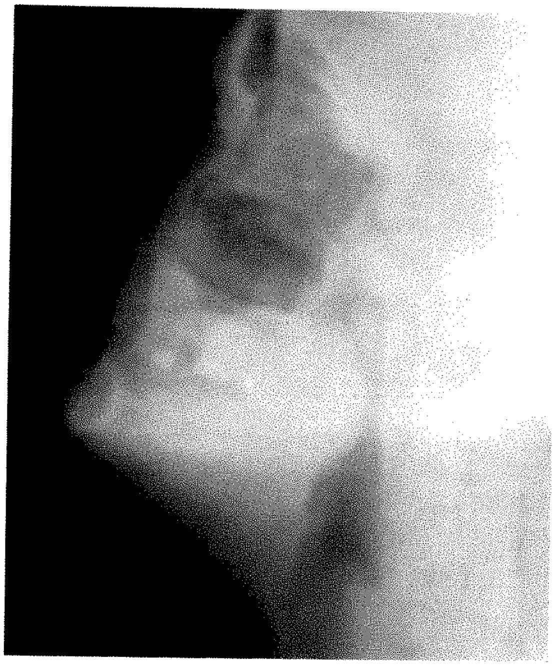

FIG. 3. Soft tissue roentgenogram showing the lower limits of a tongue lesion.

SQUAMOUS CELL CARCINOMATA

The main bulk of the tumors and the most difficult to treat were those of squamous cell origin. As with the salivary gland tumors, telecobalt therapy and 2 mev. roentgen therapy were used, and the primary tumor, the palpable lymph nodes and the proximal areas of lymph drainage were treated. If no lymph node metastases were obvious, "prophylactic" irradiation of both sides of the neck up to and including the mid-cervical region was undertaken. Retrospective examination of these patients has shown that a high dose of radiation, at least 6,500 r, is generally necessary, and also that the response is slow. Therefore, the usual 1 month interval, which one customarily allows to elapse between the end of treatment and the assessment of its success, may not be long enough. Provided the tumor is regressing and the patient is kept

TABLE VI

THE ROYAL MARSDEN HOSPITAL
TUMORS OF THE BASE OF TONGUE
1945–1962
INCIDENCE OF LYMPH NODE METASTASES

Previously Untreated Cases
Squamous Cell and Anaplastic Tumors

Site	No Lymph Node Metastases		Unilateral Lymph Node Metastases		Bilateral Lymph Node Metastases		Total	
	Squamous Cell	Anaplastic	Squamous Cell	Anaplastic	Squamous Cell	Anaplastic	Squamous Cell	Anaplastic
Posterior One-third of Tongue	12	4	23	6	14	2	49	12
Vallecula	19	4	30	8	16	4	65	16
Linguo-Tonsillar Sulcus	8	2	43	5	6	2	57	9
Totals	39	10	96	19	36	8	171	37
Total of Squamous Cell and Anaplastic Tumors	49		115		44		208	

under observation, it is justifiable to wait 6 or even 8 weeks before deciding whether or not further treatment is required. This supplementary treatment may be of various kinds—interstitial irradiation, diathermy, or radical surgery.

Interstitial irradiation can, in theory, be given either by radium needles or gold grains. In practice, we have found that radium needles are difficult to use satisfactorily, and gold grain implantation of a small residual area of disease may give good results. However, depending on the site of the residuum, diathermy may be more satisfactory, but the risk of the patient developing a necrotic ulcer is great. Radical surgery consisting of a laryngopharyngectomy with partial glossectomy has been performed in 7 cases, and, for the younger fit patients, possibly represents the best chance of a long term survival if irradiation has not been completely successful.

Complications due to radiotherapy may be necrosis of the tongue or mandible, or even myelitis due to damage to the spinal cord. Fortunately, however, our only complication has been the occasional small necrotic ulcer which usually responds well to antibiotics and good oral hygiene.

TEETH

Since the advent of antibiotics, it has not been customary to extract all teeth in patients undergoing radiotherapy to the mouth and throat. Carious teeth are removed together with any metallic fillings, and an energetic attempt is made to clean the buccal cavity. Some of these patients subsequently have developed caries of all the teeth, including those which had not been subjected to heavy irradiation. This may be due to a secondary effect of radiation on the saliva. Patients whose teeth have been removed with care and who received antibiotics have shown no incidence of osteomyelitis, and it seems preferable to give the patients a chance of surviving with their own teeth rather than removing them arbitrarily at the beginning. This latter procedure also has the disadvantage

Table VII
THE ROYAL MARSDEN HOSPITAL
TUMORS OF THE BASE OF TONGUE
1945–1962
NEW PATIENTS TREATED (250)

Radiotherapy	Posterior One-third of Tongue	Vallecula	Linguo-Tonsillar Sulcus	Total
Roentgen Ray	32	25	15	72
Teleradium, Telecobalt	26	47	33	106
Roentgen Ray+Teleradium, etc.	10	13	13	36
Interstitial Radiation	3	—	1	4
Roentgen Ray, Teleradium+Interstitial Radiation	10	3	19	32
Total	81	88	81	250
Operations				
Diathermy	8	4	8	20
Radical Surgery	3	3	1	7
Excision of Lymph Node	2	—	—	2
Block Dissection	10	4	6	20
Chemotherapy	1	—	1	2

Table VIII
THE ROYAL MARSDEN HOSPITAL
TUMORS OF THE BASE OF TONGUE
1945–1959
THREE YEAR SURVIVAL RATES ACCORDING TO SITE AND HISTOLOGY

Previously Untreated Cases

Site	Squamous Cell	Anaplastic	Sarcomas	Salivary Gland Tumor	Negative or No Biopsy	Total
Posterior One-third of Tongue	10/40 (8M:2F)	4/11 (4M:0F)	4/8 (4M:0F)	3/4 (2M:1F)	1/5 (0M:1F)	22/68 33% (18M:4F)
Vallecula	6/58 (5M:1F)	8/10 (7M:1F)	0/2	—	1/4 (1M:0F)	15/74 20% (13M:2F)
Linguo-Tonsillar Sulcus	8/49 (8M:0F)	0/7	0/2	0/2	2/9 (1M:1F)	10/69 14% (9M:1F)
Total	24/147 (21M:3F) 16%	12/28 (11M:1F) 43%	4/12 (4M:0F) 33%	3/6 (2M:1F) 50%	4/18 (2M:2F) 22%	47/211 22% (40M:7F) 22%

TABLE IX

THE ROYAL MARSDEN HOSPITAL
TUMORS OF THE BASE OF TONGUE
1945–1957
FIVE YEAR SURVIVAL RATES ACCORDING TO SITE AND HISTOLOGY

Previously Untreated Cases

Site	Squamous Cell	Anaplastic	Sarcomas	Salivary Gland Tumor	Negative or No Biopsy	Total
Posterior One-third of Tongue	7/34 (6M:1F)	2/10 (2M:0F)	2/8 (2M:0F)	2/3 (1M:1F)	0/4	13/59 22% (11M:2F)
Vallecula	4/49 (3M:1F)	2/8 (2M:0F)	0/2	—	1/4 (1M:0F)	7/63 11% (6M:1F)
Linguo-Tonsillar Sulcus	3/37 (3M:0F)	0/5	0/2	0/1	1/8 (1M:0F)	4/53 7% (4M:0F)
Total	14/120 (12M:2F) 11.6%	4/23 (4M:0F) 17%	2/12 (2M:0F) 16.6%	2/4 (1M:1F) 50%	2/16 (2M:0F) 12.5%	24/175 (21M:3F) 13%

of delaying treatment while the gums heal; also, an adequate intake of food is extremely difficult. Any carious or heavily filled back molars are always removed before treatment is started.

TABLE X

THE ROYAL MARSDEN HOSPITAL
TUMORS OF THE BASE OF TONGUE
1945–1962
THREE AND FIVE YEAR SURVIVAL RATES
ACCORDING TO SITE IN
PATIENTS WITH RECURRENCES

Squamous Cell Carcinomata

Site	Three Year Survival Rate 1945–1959	Five Year Survival Rate 1945–1957
Posterior One-third of Tongue	1/2	0/2
Vallecula	0/3	0/2
Linguo-Tonsillar Sulcus	0/2	0/2
Total	1/7	0/6

TYPES OF TREATMENT

Table VII shows the treatment, or types of treatment, given to the patients included in this series. The lymph node excisions were done as a diagnostic procedure, when no primary tumor could be found initially. Subsequently, salivary gland tumors of the base of the tongue were observed in each of these patients.

RESULTS

Table VIII shows the 3 year survival rates by site and histology. The most important factors influencing survival are histology, the presence of metastatic lymph nodes, the site of the tumor and the duration of symptoms. It will be noted that the over-all survival rate for all tumors is 22 per cent. The apparently high survival rate in the group of anaplastic tumors is possibly a statistical anomaly due to the small number of patients treated. Of the 4 patients with sarcomata who survived, 1 had a lymphosarcoma and 3 had a reticulosarcoma. It is important to note that of the 47 patients who survived 3 years, 9 had surgery (1 had

Table XI
THE ROYAL MARSDEN HOSPITAL
TUMORS OF THE BASE OF TONGUE
1945–1962
THREE AND FIVE YEAR SURVIVAL RATES ACCORDING TO THE PRESENCE OR ABSENCE OF LYMPH NODE METASTASES

Previously Untreated Cases
Squamous Cell and Anaplastic Tumors

Site	Three Year Survival Rate 1945–1959				Five Year Survival Rate 1945–1957			
	No Lymph Node Metastases	Unilateral Lymph Node Metastases	Bilateral Lymph Node Metastases	Total	No Lymph Node Metastases	Unilateral Lymph Node Metastases	Bilateral Lymph Node Metastases	Total
Posterior One-third of Tongue	3/14	10/24	1/13	14/51 (27%)	3/11	6/22	0/11	9/44 (20%)
Vallecula	7/18	6/33	1/17	14/68 (20%)	4/13	2/32	0/12	6/57 (20%)
Linguo-Tonsillar Sulcus	3/9	5/41	0/6	8/56 (14%)	1/4	2/32	0/6	3/42 (7%)
Total	13/41 (31%)	21/98 (21%)	2/36 (5%)	36/175 (20%)	8/28 (28%)	10/86 (11%)	0/29	18/143 (12%)

a block dissection plus diathermy, 3 a block dissection and lateral pharyngectomy, 2 a block dissection only and 3 had radical surgery—1 of these being for salivary gland tumor.) Thirty-eight patients survived without surgery; it, therefore, seems that treating these patients with radiotherapy first saved a large number of patients from unnecessary mutilation and yet did not prevent surgery from being done when necessary.

The 5 year survival rates (Table ix) show a drop from the over-all figure of 22 per cent to 13 per cent, and the results in the anaplastic group more nearly approached those of the squamous cell group. The 2 sarcomata were lymphosarcoma and reticulosarcoma. Four patients only out of 24 had surgery; 1 had a block dissection and lateral pharyngectomy, 1 a block dissection only, and 2 had radical surgery to the primary site, the latter being for salivary gland tumor.

In Table x the 3 and 5 year survival results of the patients with recurrences are shown.

In Table xi results are tabulated according to the presence or absence of metastatic lymph nodes. At 3 years the survival rate when disease was confined to the primary site was 31 per cent, dropping only to 28 per cent at 5 years. It is interesting that the results are much better in the patients with lesions of the posterior one-third of the tongue than in those with lesions of the vallecula or linguo-tonsillar sulcus; tumors of the linguo-tonsillar sulcus have the worse prognosis, possibly due to the insidious onset and the rapidity with which they metastasize to lymph nodes.

The size of the lymph node does not seem important. An attempt was made to

TABLE XII

THE ROYAL MARSDEN HOSPITAL

TUMORS OF THE BASE OF TONGUE

1945–1962

INFLUENCE OF DURATION OF SYMPTOMS ON THREE AND FIVE YEAR SURVIVAL RATES

Previously Untreated Cases

Duration	Three Year Results (1945–1959)				Five Year Results (1945–1957)			
	Posterior One-third of Tongue	Vallecula	Linguo-Tonsillar Sulcus	Total	Posterior One-third of Tongue	Vallecula	Linguo-Tonsillar Sulcus	Total
Up to 6 mo.	16/49	7/52	7/48	30/149 (20%)	11/42	1/41	3/35	15/118 (12%)
Up to 1 yr.	3/15	6/15	1/16	10/46 (21%)	1/14	4/15	1/14	6/43 (13%)
Over 1 yr.	3/4	2/7	2/5	7/16 (43%)	1/3	2/7	0/4	3/14 (21%)
Total	22/68 (32%)	15/74 (20%)	10/69 (10%)	47/211 (22%)	13/59 (22%)	7/63 (11%)	4/53 (7%)	24/175 (13%)

divide the cases into two groups; those with lymph nodes less than 2 cm. and those with lymph nodes greater than 2 cm. The prognosis did not improve when the metastasis was small.

In Table XII, the results are compared with the duration of symptoms. In lesions of the base of the tongue, as in other sites, early diagnosis does not necessarily mean cure; in fact, it appears that the results are better, when the patient does not seek early medical advice. This, of course, indicates that such patients have a slow-growing tumor with few symptoms and a long natural history. Thus, tumor type seems to be the most important factor in the treatment of this disease and improvement in results is more likely to be obtained by the radiobiologist who can perhaps alter the characteristics of the tumor, rather than by advances in surgery or radiotherapy.

SUMMARY

A series of 265 patients with tumors of the base of the tongue was studied. The tumors occur most commonly in older patients, and lymph node metastases appear early. These two factors tend to make radiotherapy the initial treatment of choice; however, the use of surgery following radiotherapy may improve the survival rate, especially of young patients.

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My thanks are due to the Staff of The Royal Marsden Hospital and the Staff of The Royal National Throat, Nose and Ear Hospital, London, for permission to publish these cases; to Dr. M. Lederman, by whom most of these patients were treated; to Dr. N. F. C. Gowing, Pathologist at The Royal Marsden Hospital, who reviewed most of the slides; and to the Medical Art and Photographic Departments of The Royal Marsden Hospital, who produced the tables and illustrations.

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MANAGEMENT OF RESIDUAL OR RECURRENT CANCER FOLLOWING RADIATION THERAPY FOR SQUAMOUS CELL CARCINOMA OF THE OROPHARYNX*

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INFORMATION on the surgical management of residual cancer of the oropharynx after radiation therapy is relatively sparse. It seemed worthwhile, therefore, to review the experience at M. D. Anderson Hospital with oropharyngeal cancer, from the opening of the institution in 1944 until December, 1962, in order to determine the rate of failure to control the primary tumor by irradiation and to assay the value of a surgical approach in these cases. The over-all experience is summarized in Table I. It is apparent that most of the patients with malignant lesions in this anatomic site are initially referred to undergo radiation therapy. Eighty to ninety per cent of the patients were treated with a cobalt 60 unit or a 22 mev. betatron with tumor doses of 6,000 to 7,000 rads in 5 to 7 weeks.

Residual or recurrent cancer may be clinically evident upon completion of radiation therapy, or may not become apparent for many years. Although 11½ years had been the longest interval in this series, 80 per cent of residual or recurrent diseases are clinically manifest at 1 year and 90 per cent at 2 years.

The staging of the primary cancer and lymph node metastasis is as follows:

T1—Tumors less than 3 cm. in diameter
T2—Tumors 3 to 5 cm. in diameter, with minimal extension to adjacent structures
T3—Tumors more than 5 cm. in diameter, with limited or moderate extension to adjacent structures
T4—Massive primary tumor
N0—No clinical evidence of lymph node metastasis
N1—Clinically evident single lymph node metastasis less than 3 cm. in diameter
N2—Single lymph node metastasis over 3 cm. in diameter, or multiple ipsilateral lymph node metastases
N3—Large lymph node metastasis with fixation, or bilateral metastases

Based on this staging, the rate of local control of the primary tumor is shown in Table II and Table III, both by stage of the primary lesion and by anatomic site. As would be expected, the success of local control varies inversely with the size of the primary tumor. There is no difference in the recurrence rate for the various anatomic sites with the exception of the pharyngeal walls. In that location, there is a higher recurrence rate for the T3 and T4 lesions.

Almost half of the recurrences were extirpated. The incidence of surgical management was higher for recurrences in the T1 and T2 groups. There is greater number of surgical management of the recurrences in the T3 group for the anterior faucial pillar, retromolar trigone, the soft palate, and tonsillar fossa. Recurrences in the base of the tongue are not as often surgically managed; the same applies to the T3 and T4 lesions of the pharyngeal walls.

The reasons that surgical management was not employed for some of the recurrences were several—poor general condition of the patient, presence of distant metastases, refusal of treatment, or be-

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TABLE I

CANCER OF THE OROPHARYNX
1944–1962
PRIMARY TREATMENT

Site	Total	Surgery	Irradiation	No Treatment
Anterior Faucial Pillar Retromolar Trigone	142	16	122	4
Soft Palate	59	1	54	4
Tongue (base)	146	4	131	11
Tonsillar Fossa	102	—	98	4
Pharyngeal Walls	147	31	108	8
Total	596	52	513	31

cause the scope of the disease was too massive. Since healing may be delayed when surgical intervention follows radiation therapy, it is important that patients selected for operation be in a satisfactory nutritional state. Tube feedings, blood and plasma transfusions and other supportive measures should be employed liberally in order to put the patient in optimal condition for surgery.

TYPES OF SURGICAL PROCEDURE

All patients in this series had recurrent cancer in the primary site after radiation therapy in this institution and all also had some type of surgical procedure to remove the local tumor. In addition, most had either simultaneous or staged removal of the cervical lymph nodes. If clinically positive lymph nodes were present at the time of the first examination and if these lymph nodes were large or fixed, a combined operation was done even though, at the time of detection of the recurrence in the primary site, clinical lymphadenopathy was no longer present. This approach is based on the observation that if the primary lesion were not controlled by irradiation, large metastatic lymph nodes would also probably not be controlled. In all except 3 cases of recurrent cancers of the soft palate and a few of the base of tongue, a combined operation included neck dissection with resection of the mandible and removal of the primary tumor in continuity. Mucosal closure in these procedures was effected either by primary approximation or by the use of skin grafts. The use of skin grafts is somewhat hazardous after irradiation, particularly if the dose to the primary tumor has exceeded 6,000 rads. If a large area of mucosa was resected and the tissues considered unsuitable for the application of a split thickness skin graft, a stoma was created by suturing mucosa to skin. Such a stoma was later closed by migration of a tube pedicle from a distant site.

In all patients treated surgically after irradiation, the prime concern is adequate coverage of the carotid artery. This is not a major cause of concern in recurrences of the retromolar trigone and anterior tonsillar pillar or with lesions of the tonsillar fossa. However, in lesions of the base of the

TABLE II

CANCER OF THE OROPHARYNX
1944–1962
RECURRENCES TREATED BY SURGERY IN PRIMARY IRRADIATION GROUP
SUMMARY BY STAGE

Stage	Total in Site	No. with Recurrences	Recurrences Treated by Surgery
T_1	74	7 (9.5%)	5
T_2	141	19 (13.5%)	11
T_3	163	37 (22.7%)	22
T_4	134	47 (35.1%)	16

tongue, and particularly of the pharyngeal walls, this becomes of prime concern. In surgical removal of recurrences in these locations, the carotid may be covered with dermal graft after the method of Corso and Gerold,[1] by use of the levator scapulae muscle as advocated by Schweitzer,[2] or by skin flaps which would then result in creating a pharyngeal stoma.

COMPLICATIONS OF SURGERY

Delayed wound healing is to be expected in an appreciable number of these patients, as seen in Table IV. A neck dissection alone, after irradiation, can be accomplished with minimum risk and with little fear of delayed healing as long as the skin flaps are handled gently and particularly if the dissection is done through a single curved vertical incision rather than through a trifurcate incision. The incidence of complications increases with the magnitude of the mucosal resection, but the risk does not become major until the pharyngeal wall is resected. In this area, delayed wound healing may be anticipated even with local removal, for the prevertebral fascia is incapable of contracting to close a defect. If primary union does not occur, the risk of exposure of the carotid vessels becomes great. The incidence of delayed wound healing and other wound complications may be reduced by the adequate replacement of blood at the time of the operation and maintenance of proper nutrition during the postoperative period. Antibiotics should be administered preoperatively and during the postoperative period, since irradiated tissues are less resistant to infection.

Table III

CANCER OF THE OROPHARYNX
1944–1962
RECURRENCES IN PRIMARY IRRADIATION GROUP

Site	Stage	Total in Site	No. with Recurrence	Recurrences Treated by Surgery
Anterior Faucial Pillar Retromolar Trigone	T1	16	2	2
	T2	56	8	5
	T3	36	6	6
	T4	14	5	1
Total		122	21	14
Soft Palate	T1	22	1	0
	T2	12	1	1
	T3	13	3	3
	T4	7	1	1
Total		54	6	5
Base of Tongue	T1	20	3	2
	T2	18	2	1
	T3	43	11	2
	T4	50	16	4
Total		131	32	9
Tonsillar Fossa	T1	7	0	0
	T2	31	3	1
	T3	33	5	4
	T4	27	9	6
Total		98	17	11
Pharyngeal Walls	T1	10	1	1
	T2	22	5	3
	T3	39	12	7
	T4	37	16	4
Total		108	34	15
Grand Total		513	110	54

ESTIMATE OF THE SIZE OF THE RESIDUAL TUMOR

When a large oropharyngeal tumor has been irradiated and only a small residuum is detected later, the tendency is to remove only a limited volume of tissue around the residual mass. However, if the initial primary tumor was large and very infiltrative, the residual tumor may actually be more extensive than is clinically apparent, and may approximate, or even exceed, the size of the tumor initially observed. This is illustrated by the following case report.

ILLUSTRATIVE CASE

Case 1. A 60 year old white woman was ini-

TABLE IV

CANCER OF THE OROPHARYNX
1944–1962
TYPE OF SURGERY AND WOUND HEALING

Site	Combined Neck Dissection and Resection of Primary Lesion In Continuity		Neck Dissection and Discontinuous Resection of Primary Lesion		Resection of Primary Lesion		Other	
	Delay	No Delay	Delay	No Delay	Delay	No Delay	Delay	No Delay
Anterior Faucial Pillar Retromolar Trigone	5	2	1	—	3	1	2	—
Soft Palate	—	1	—	2	—	2	—	—
Base of Tongue	5*	—	—	—	—	3	—	1
Tonsillar Fossa	6	3	1	—	—	1	—	—
Pharyngeal Walls	6**	1	—	—	5	3	—	—
Total	22	7	2	2	8	10	2	1

* Three nonfatal carotid perforations with ligation; 1 fatal carotid hemorrhage.
** Three fatal carotid perforations.

tially seen on December 17, 1958 with a large infiltrative lesion of the posterior pharyngeal wall estimated to be 5 cm. in diameter. A clinically positive lymph node, 3.5 cm. in diameter, was palpable in the right subdigastric area and a smaller lymph node was present in the left subdigastric area with an additional lymph node lower in the jugular chain. Biopsy examination of the pharyngeal lesion showed squamous cell carcinoma, Grade III. From December 22, 1958 to February 5, 1959, the patient received a tumor dose of 7,350 rads to the primary lesion with the cobalt 60 unit. A small area of ulceration was detected 5 months later, but this was not believed to be related to residual tumor until December, 1959. At that time, a local excision of the recurrent growth was done and a skin graft applied. Most of the skin graft sloughed, but eventually satisfactory healing occurred. Recurrence was again suspected in August, 1960 and by December, 1960 it became clinically evident that the cancer was again active throughout the original area and also in the thyroid gland. Further treatment was not possible and the patient expired on June 1, 1961.

TABLE V

CANCER OF THE OROPHARYNX
1944–1962
INFLUENCE OF POSITIVE LYMPH NODES ON OUTCOME

Site	Lymph Nodes Positive		Lymph Nodes Negative	
	Successes	Failures	Successes	Failures
Anterior Faucial Pillar Retromolar Trigone	–	2	8	3
Soft Palate	1	1	1	2
Base of Tongue	1	4	2	–
Tonsillar Fossa	5	3	2	1
Pharyngeal Walls	1	5	2	7
Total	8	15	15	13

RESULTS OF TREATMENT

The results of treatment are shown in Tables V, VI, VII, and VIII, analyzed with regard to size of the initial primary tumor and presence or absence of positive lymph nodes as determined at the time of the surgical procedure for the recurrence. The results have been classified either as success or failure, rather than given in terms of sur-

Table VI

CANCER OF THE OROPHARYNX

1944–1962

INFLUENCE OF SIZE OF PRIMARY LESION ON SALVAGE

Site	T1		T2		T3		T4		Total
	Successes	Failures	Successes	Failures	Successes	Failures	Successes	Failures	
Anterior Faucial Pillar Retromolar Trigone	1	1	5	—	2	3	—	1	13
Soft Palate	—	—	1	—	1	2	—	1	5
Base of Tongue	1	1	—	—	—	1	2	2	7
Tonsillar Fossa	—	—	1	—	3	1	3	3	11
Pharyngeal Walls	—	1	2	1	1	6	—	4	15
Total	2	3	9	1	7	13	5	11	51

vival period. Those results are classified as successful in which the patients have survived a year or more without evidence of recurrence at the site of the primary treatment. Some of these patients may develop evidence of recurrence later.

Results have been classified as failures in which a recurrence has developed within the field of the primary tumor at any time or when the patient has died within a year of whatever cause.

A third small group of indeterminate results comprise those patients in whom the interval from time of operation is less than a year, but who are living without evident recurrence.

In general, it may be seen that the smaller the initial presenting lesion, the fewer the metastatic lymph nodes; and the longer the time interval between the radiation treatment and the operation for the recurrence, the better the result is likely to be. The greater success rate in those patients whose recurrences were treated after

Table VII

CANCER OF THE OROPHARYNX

1944–1962

INFLUENCE OF TIME INTERVAL FROM COMPLETION OF IRRADIATION TO SURGICAL PROCEDURE ON SALVAGE

Site	Time Interval in Months										Total
	1–3		3–6		6–12		12–24		24+		
	Successes	Failures	Successes	Failures	Successes	Failures	Successes	Failures	Successes	Failures	
Anterior Faucial Pillar Retromolar Trigone	3	1	—	2	2	1	1	1	2	—	13
Soft Palate	1	2	1	1	—	—	—	—	—	—	5
Base of Tongue	—	1	1	2	1	1	—	—	1	—	7
Tonsillar Fossa	3	3	1	—	3	1	—	—	—	—	11
Pharyngeal Walls	—	4	1	2	1	4	1	1	—	1	15
Total	7	11	4	7	7	7	2	2	3	1	51

TABLE VIII

CANCER OF THE OROPHARYNX
1944–1962
SURGERY FOR RESIDUAL TUMOR
AFTER IRRADIATION

Site	Successes	Failures	Indeterminate	Total
Anterior Faucial Pillar Retromolar Trigone	8	5	1	14
Soft Palate	2	3	0	5
Base of Tongue	3	4	2	9
Tonsillar Fossa	7	4	0	11
Pharyngeal Walls	3	12	0	15
Total	23	28	3	54

6 months reflects the biologic weeding out of the more unfavorable tumors in which recurrence is detected early. Also, it is quite apparent that with progression posteriorly in the oropharynx, the poorer the result is likely to be with surgical intervention for recurrent tumor after irradiation. The successes with recurrent pharyngeal wall cancer are few and the complications many. There are probably several reasons for this: (1) high pharyngeal wall lesions which approach the nasopharynx are difficult of surgical access; (2) the incidence of positive retropharyngeal lymph nodes in pharyngeal wall cancer is high, and an extensive retropharyngeal lymph node dissection is approached with trepidation after irradiation because of the necessity of stripping the internal carotid artery to the base of the skull; (3) it is difficult to provide adequate coverage for the carotid arteries after extensive removal of the pharynx when the area has been previously irradiated. This, of course, accounts for the relatively high incidence of serious complications in this group.

TRENDS

Experience over the years has revealed that some oropharyngeal cancers can be successfully treated after irradiation. There has been an increasing tendency at M. D. Anderson Hospital to re-evaluate the lesion toward the end of the therapy course with a view to terminating treatment earlier if resolution of the primary lesion is not satisfactory. Such a course can be illustrated by the following case report.

ILLUSTRATIVE CASE

CASE II. A 47 year old white man who was an alcoholic and a heavy smoker was seen initially on November 6, 1962 with a lesion of the tonsillar fossa extending into the anterior tonsillar pillar and the adjacent base of tongue. A group of lymph nodes was palpable in the left subdigastric area. The lesion was staged as T_3N_2. The biopsy study showed squamous carcinoma, Grade III. From November 8, 1962 to December 19, 1962, utilizing the cobalt 60 unit and the 22 mev. betatron, a tumor dose to the primary lesion of 5,700 rads was delivered. During the course of treatment, it was observed that the regression of both the primary lesion and the metastatic lymph nodes was less than would be anticipated, so treatment was stopped short of the initially set goal. On February 4, 1963, left neck dissection, resection of mandible, tonsillar region, contents of pterygoid fossa, base of tongue and a portion of pharyngeal wall was done. The pathologic report showed residual squamous cell carcinoma in tonsillar region, base of tongue, pharyngeal wall and palate with metastatic squamous cell carcinoma in 2 of 12 subdigastric and 1 of 10 lower jugular lymph nodes. The defect in the pharyngeal wall was closed by a skin flap to cover the carotid artery. Subsequently, an acromiothoracic tube pedicle was migrated in to close the pharyngeal stoma. An obturator was fitted, to close the palatal defect. The patient now eats and talks without difficulty, and there was no evidence of recurrence when seen on February 4, 1964.

Because of the relatively high recurrence rate in extensive pharyngeal wall lesions and the difficulties in dealing with recurrences in this area by surgical procedures following irradiation, surgical removal is being employed more frequently initially in the management of large infiltrative lesions. The value of surgical therapy as the initial form of treatment for extensive cancer in other areas of the oropharynx remains to be explored.

CONCLUSIONS

1. Operation for residual cancer following radiation therapy for oropharyngeal cancer is feasible.

2. The risk of operation is not prohibitive, although healing may be delayed and multiple procedures may be required for closure of fistulas.

3. Salvage rate is reasonable for patients with the more anterior lesions but poor for those with cancers involving pharyngeal walls.

4. Initially extensive oropharyngeal cancers recurrent after irradiation tend to be more extensive than a small clinical recurrence would indicate.

5. When large oropharyngeal cancers do not respond well during irradiation, reduction of anticipated dose to be followed by operation should be done.

6. A surgical approach should be considered as the initial therapy for large invasive lesions of the pharyngeal walls.

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MALIGNANT TUMORS OF THE NASOPHARYNX

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MALIGNANT disease of the nasopharynx has become increasingly important to those dealing with diseases of the head and neck. It is of greatest concern to the otolaryngologist and therapeutic radiologist; however, it may arise as a possibility in the differential diagnostic consideration of the internist, ophthalmologist, and neurologist as well.

The purpose of the author is to present a series of 44 cases of pathologically proven primary malignant disease of the nasopharynx seen at the New York Hospital-Cornell Medical Center from 1940 through 1958, along with a general discussion of this disease.

GENERAL CONSIDERATIONS

Malignant disease of the nasopharynx was first recognized and reasonably confirmed histologically as early as the middle of the 19th century.[17] Although subsequent reports[8,11] appeared in which the entity was better defined, the first report of significance was published in 1911.[24] Regaud,[20] and in 1921 Reverchon and Coutard,[21] and Schmincke[22] documented lymphoepithelioma as a histologic entity. As to whether this is or is not a true histostructural entity is still a matter of controversy among histopathologists.

Malignant disease of the nasopharynx constitutes 1 to 2 per cent of all malignant disease[9,13,19,25] and 14 per cent of all malignant disease of the pharynx (oropharynx 40 per cent, laryngopharynx 46 per cent.)[18]

It is well recognized that racial predisposition exists. Orientals (excepting the Japanese) have a higher incidence of nasopharyngeal cancer (in which, histologically, there is a strong incidence of lymphoepithelioma) than any other racial group.[18,16,25,26,28] On the other hand, there is a higher incidence of oropharyngeal cancer in India than in other parts of the world, and a higher incidence of cancer of the hypopharynx in Scandinavia than in other areas.[13] Lederman also found a higher incidence among Maltese patients. Sex predilection is 2:1 in favor of males, both in Orientals and non-Orientals. In general, the mean age of occurrence of the disease is lower in women than in men, again this being true of the Oriental group as well as the Caucasian. Finally, the Orientals as a group develop the disease at an earlier age than non-Orientals.[23]

PATHOLOGY

These lesions can be classified grossly into (1) ulcerative (or ulcero-invasive); (2) polylobulated; and (3) exophytic. The ulcerative and lobulated varieties have a greater tendency to invade and erode locally than does the exophytic variety. Microscopically, the following types are found: (1) well differentiated epidermoid carcinoma (squamous cell type); (2) anaplastic or undifferentiated carcinoma (in most series more common than epidermoid); (3) transitional cell carcinoma, which is regarded by some as a true variant of the undifferentiated type; (4) lymphoepithelioma; (5) lymphosarcoma; and (6) reticulum cell sarcoma. Less frequently chordoma, rhabdomyosarcoma, plasmacytoma,[10,15] mixed mucous and salivary gland tumor becoming an adenocarcinoma (arising from soft palate floor of nasopharynx) are noted; and very rarely fibrosarcoma or osteogenic sarcoma arising from the base of the skull may occur.

As already indicated, many pathologists[23,27] regard lymphoepithelioma as an undifferentiated carcinoma with slight alteration in the microscopic picture due to the infiltration of lymphocytes. This thesis, however, is rather difficult to accept since tumors classified as lymphoepithelioma exhibit a distinctly better prognosis (provided that they have not metastasized to distant sites) than the undifferentiated lesions.

SPREAD

Regional lymphatic extension of these tumors is to: (1) the retropharyngeal lymph nodes; (2) the internal jugular chain; and (3) the spinal chain in the posterior cervical triangle. Distant hematogenous metastases are the exception in the well differentiated epidermoid carcinomas, which usually are of the ulcero-invasive type, invading and destroying local mucosa, fascia, nerves, bone, and intracranial structures. The undifferentiated carcinomas and lymphoepitheliomas have a far greater tendency to distant disemination, metastasizing to lungs, bones, liver, testicle, and other organs.[7,12] The lymphosarcomas eventually extend to the supraclavicular fossae, axillae, mediastinum, spleen, and bone marrow; *i.e.*, in the direction of systemic involvement which, when unchecked, represents the natural course of events in lymphomatous disease.

CLINICAL EVOLUTION AND DIAGNOSIS

The nasopharynx has been called the great "blind spot" in the diagnosis of tumors of the head and neck.[1,6,14] New[18] reported that in 194 patients with malignant tumors of the nasopharynx, 185 operations were performed before the correct diagnosis was established. Surgery was used on sinuses, turbinates, ear drum, mastoids, teeth, and nasal polyps. Many of these errors might have been avoided had a sufficiently high index of suspicion been directed at the nasopharynx. However, in some cases where the nasopharynx had been examined, the true pathologic process was not uncovered because the surface lesion was inflammatory, and was diagnosed as such by mucosal biopsy, while the invasive neoplastic process had been lying beneath. A deeper biopsy would have revealed the tumor.

The majority of patients with lesions at this site is seen because of cervical lymphadenopathy without any symptoms referable to a primary lesion in the nasopharynx. The next most common presenting symptoms are impaired hearing, nasal obstruction, cranial nerve signs, and pain. The lymph node involvement usually presents as a unilateral painless upper cervical lymphadenopathy; very often the jugulodigastric lymph nodes in the mastoid region are the first to become affected. Lymph nodes farther down in the internal jugular chain group, deep to the sternocleidomastoid muscle, may likewise become involved, as may the retropharyngeal lymph nodes and those of the posterior spinal chain in the posterior cervical triangle. In those lesions which are undifferentiated, the lymph nodes may become considerably enlarged and lobulated. In the well differentiated lesions, the lymph node swellings are smaller and more round. Where the primary lesion is a lymphosarcoma, the cervical lymph node involvement is often bilateral, the process may extend quite rapidly to neighboring lymph nodes in the neck, and the lymph nodes are usually softer. Hypoacusia, when seen, is usually unilateral, and due to the obstruction of the orifice of the eustachian tube. Nasal obstruction, which may cause a nasal speech twang, is quite common. Bloody nasal discharge is less common, but may be seen.

Godtfredsen[9] found 38 per cent of adults presenting with neurologic symptoms. The number is doubled in children. Most frequently involved are nerves III, IV, V, VI, IX, and X; less frequently I, II and XII; and VII and VIII even less frequently. The cervical sympathetic chain likewise may be affected by high cervical lymph node involvement. When the cranial nerves are affected, it is usually as a combination of the fourth and fifth nerves; however, a unilateral involvement of all 12 cranial nerves has sometimes been observed with advanced cancer of the nasopharynx. This may be seen when basal skull invasion and destruction are marked and extensive, such as in osteogenic sarcoma or fibrosarcoma.

TABLE I

CASES TREATED AT THE NEW YORK HOSPITAL—CORNELL MEDICAL CENTER

	No. of Patients
Race	
Caucasian	38 (86.4%)
Oriental	4 (9.1%)
Negro	2 (4.5%)
Age	
Under 40 years	6 (13.6%)
40 to 49 years	14 (31.8%)
50 to 59 years	14 (31.8%)
60 years and over	10 (2.3%)
Sex	
Males	32 (72.7%)
Females	12 (27.3%)

The natural history of malignant tumors of the nasopharynx, which are not brought under control, is toward generalization of the disease. In well differentiated epidermoid carcinoma, however, local invasion of the base of the skull,[2–5] meningeal involvement, hemorrhage, secondary infection, and severe pain lead to a general deterioration and death, very commonly without distant metastases. In the anaplastic (or undifferentiated) group, distant spread to the bones, lungs and liver is seen. The same holds true for the lymphoepitheliomas. In lymphosarcoma, there is eventual involvement of the entire lymphatic and reticuloendothelial system.

CASE MATERIAL

This study consists of a series of 44 biopsy proven cases of primary malignant disease of the nasopharynx, seen and treated at the New York Hospital—Cornell Medical Center from 1940 through 1958. Eleven cases were discarded because evidence that they represented primary disease of the nasopharynx was lacking. Disseminated lymphomas were likewise discarded. In evaluating the results, the patients lost to follow-up were presumed dead of their malignant disease as of the date when last seen (even if alive and clinically free of disease when last seen). Those who died, and where the cause of death was not known for certain, too, were presumed dead of their malignant disease.

RACIAL INCIDENCE

Thirty-nine of the patients were Caucasian; 4 were Chinese (9.1 per cent). Considering that less than 1 per cent of the population of New York City is Oriental, this, then, is significant of the unusually high incidence of malignant disease of the nasopharynx in this group. In San Francisco, where the Chinese population represents 4 per cent of the total, Vaeth[25] found an incidence of 17 per cent Chinese in a series of 82 patients. Two of our patients were Negroes.

SEX INCIDENCE

Thirty-two males and 12 females (approximately the ratio of males to females noted in most other reports[18,25,26]) comprised the series.

AGE INCIDENCE

The ages of the patients when first seen ranged from 8 to 72 years. The majority was in the fifth and sixth decades, 31.8 per cent each, respectively. The average age of the males in our group was 50.4 years and of the females 49.5 years (Table I).

HISTOLOGY

The histologic varieties in our series ranged over the type-spectrum seen in the majority of other series, although our incidence of lymphoma cases was somewhat lower. Of a total of 218 cases of primary nasopharyngeal malignancy, Lederman[18] reported 20 cases of reticulum-cell sarcoma and 14 cases (15.6 per cent) of lymphosarcoma. Of the 82 cases studied by Vaeth,[25] 4 (4.9 per cent) were lymphosarcoma. Of 115 cases evaluated by Want *et al.*,[26] 8 (6.9 per cent) were classified as malignant lymphoma. In the present series, there was 1 lymphoma classified as a reticulum-cell sarcoma (2.3 per cent). In several series no distinct histologic differentiation is made between undifferentiated carcinoma and transitional-cell carcinoma; instead, they are grouped together in either one or the other category. In this group the pathology department did make such a microscopic distinction and therefore the incidence for either type differs from that cited by others who used a single designation. The lymphoepitheliomas were considered a separate entity and our incidence of this lesion is similar to that reported in other studies (Table II).

CLINICAL FINDINGS

The clinical findings have been tabulated in their descending order of frequency at the initial evaluation (Table III). The incidence of roentgenographic evidence of basal skull invasion is placed separately at the bottom of the list because it is not truly a clinical symptom or sign.

Cervical lymphadenopathy was the most frequently encountered initial clinical feature, followed by cranial nerve signs, headache, loss of hearing, and nasal obstruction, in that order. Headache frequently existed without any specific cranial nerve signs and cannot, therefore, be regarded by itself as evidence of cranial nerve involvement. Loss of hearing may generally be regarded as the result of eustachian orifice blockage, rather than the result of eighth nerve involvement. Likewise, tinnitus is not due to eighth nerve involvement, but is an effect of the presence of tumor in the nasopharynx. Fifteen (34.1 per cent) of our patients had demonstrable roentgenographic evidence of local skull destruction on initial evaluation.

Table II

HISTOLOGIC CLASSIFICATION OF PATIENTS

Histology	No. of Patients	Per Cent of Total Series
Epidermoid carcinoma	15	34.0
Undifferentiated carcinoma	12	27.3
Lymphoepithelioma	8	18.2
Transitional-cell carcinoma	5	11.4
Reticulum-cell sarcoma	1	2.3
Adenocarcinoma arising from a previous mixed salivary gland tumor	1	2.3
Chordoma	1	2.3
Rhabdomyosarcoma	1	2.3
Total	44	100.0

Table III

PRESENTING SYMPTOMS WHEN FIRST SEEN

	No. of Patients	Per Cent
Cervical lymphadenopathy	25	56.8
Cranial nerve signs diplopia, facial pain, facial palsy, hoarseness, dysphagia	15	34.1
Headache	14	31.8
Loss of hearing	12	27.3
Nasal obstruction	12	27.3
Bloody discharge	9	20.5
Tinnitus	6	13.6
Proptosis	1	2.3
Perforation of soft palate	1	2.3
Roentgenographic evidence of basal skull invasion	15	34.1

RADIATION THERAPY

Prior to January, 1957, patients with malignant disease of the nasopharynx were treated at this institution with orthovoltage radiation of 200–250 kv., half value layer of 1.5–2.6 mm. Cu. In 1957, we commenced treating such lesions on a 1,000 C Co^{60} unit. During the orthovoltage period, the primary lesion was irradiated through 4 fields; *i.e.*, 2 opposing temporal fields and 2 infraorbital fields. The former pair were generally 8 cm. rectangular and the latter 5 cm. diameter circular fields. Occasionally, a 3.5 cm. diameter cone was used transorally, aimed at the primary site. Where indicated, either when first seen or when there was evidence of recurrence, appropriate neck fields were employed, in some cases covering only the clinically involved lymph node areas and in others the entire neck on the involved side or sides. No neck irradiation was carried out in the absence of clinical lymph node spread. Several patients had radon seed implantation for recurrent neck lymph node involvement

TABLE IV

FACTORS CORRELATED WITH 5 YEAR SURVIVAL

	Total No. of Patients	5 Year Survivals
Sex		
Males	32	7 (21.9%)
Females	12	6 (50.0%)
Race		
Caucasian	38	12 (31.6%)
Oriental	4	1 (25.0%)
Negro	2	0
Age		
Under 40 years	6	2 (33.3%)
40 to 49 years	14	5 (35.7%)
50 to 59 years	14	4 (28.6%)
60 years and over	10	2 (20.0%)
Those presenting with no evidence of local spread	7	4 (57.1%)
Cervical lymphadenopathy	27	8 (33.3%)
Signs or symptoms due to cranial nerve involvement	19	5 (26.3%)
Roentgenographic evidence of local bone invasion (direct)	14	3 (21.4%)

which had appeared after treatment to the neck by external roentgen therapy. Of the 44 patients in the over-all series, only 2 had been subjected to cobalt 60 irradiation; these patients were treated in 1958.

The patients in the orthovoltage group received a depth dose to the nasopharynx ranging from 3,600 r to 8,500 r when first treated; the over-all time ranged from 26 days to 70 days. In those cases in which the neck was also treated, the incident skin dose to either side varied from 3,800 r to 5,600 r.

RESULTS

Of our total series of 44 patients, 13 survived 5 years or longer (29.5 per cent). Of these 13, 9 were clinically free of malignant disease at 5 years. The 4 patients who were not free of disease at the 5 year period have succumbed later. Of the 9 who were clinically free of disease, 7 are alive and clinically well as of this writing and 2 have died of other causes with no known evidence of residual disease. Of the 13 five year survivors, 7 were males and 6 were females. Thus, 21.9 per cent of all treated males and 50 per cent of the females survived 5 years—a finding noted in most other series. There were 31.6 per cent Caucasian patients in this group and 25.0 per cent Oriental patients. The published reports generally indicate a higher incidence of 5 year survivals in the Oriental patients; however, the present study did not bear this out. The fact that there were only 4 Oriental patients in the group may account for this.

Our highest incidence of 5 year survival was in patients in the fourth and fifth decades. The patients in the first and second decades showed a uniformly poor prognosis. Our 2 youngest cases, 8 years and 19 years of age, died within 6 months and 3 years, respectively, after therapy.

In evaluating the correlation between 5 year survival and local spread, 7 patients presented initially with no evidence of enlarged neck lymph nodes, cranial nerve involvement, or local bony invasion; 4 (57.1 per cent) survived 5 years or better. Of 37 who had evidence of such spread, 9 (24.3 per cent) survived 5 years or longer. From the prognostic point of view, then, the 5 year salvage is more than doubled when the patient is initially free of such spread. Of the 4 presenting with no evidence of spread, none has as yet developed local or distant dissemination (Table IV).

Histologically, the patients with lymphoepithelioma had the most favorable prognosis (62.5 per cent survivals)—a finding frequently reported by others. The undifferentiated carcinoma cases had the lowest 5 year survival rate (8.3 per cent). Others have reported the well differentiated squamous group to have a lower 5 year survival rate than the undifferentiated variety. If in the present series the transitional-cell cases were grouped with the undifferentiated cases, then the survival rate in the undifferentiated group as compared to the epidermoid group would also be higher. The patient with reticulum-cell sarcoma, the single case of chordoma and the 1 patient with rhabdomyosarcoma all died. The latter two types have a uniformly unfavorable prognosis (Table v).

Regarding the relationship between irradiation modality and survival, since only 2 patients in this study were treated by cobalt 60 teletherapy (1 has survived 5 years and is still alive and well), no valid conclusion can be drawn at this time as to the effect of the method of treatment on survival. In the reported series, the therapeutic approach was, in general, quite similar in all patients.

In 2 instances postradiation complications were noted; both patients were in the 5 year survival group. One, a 56 year old white male, was treated on the 250 kv. unit in 1942 for an epidermoid carcinoma. At that time there was evidence of cranial nerve involvement as well as unilateral neck lymph node involvement. A depth dose of 8,000 r in 40 days was delivered to the nasopharynx. He died of a cerebral abscess 8 years later. This was secondary to postradiation necrosis of the maxilla, sphenoid and temporal bones. Postmorten examination showed no evidence of residual malignant disease.

TABLE V

RELATIONSHIP OF HISTOLOGY AND 5 YEAR SURVIVAL

Histology	No. of Patients	5 Year Survival	Per Cent of All 5 Year Survivals
Epidermoid carcinoma	15	4 (26.7%)	30.8
Undifferentiated carcinoma	12	1 (8.3%)	7.7
Lymphoepithelioma	8	5 (62.5%)	38.5
Transitional-cell carcinoma	5	2 (40.0%)	15.4
Adenocarcinoma arising from a previous mixed salivary gland tumor	1	1 (100.0%)	7.7
Reticulum-cell sarcoma	1	—	—
Chordoma	1	—	—
Rhabdomyosarcoma	1	—	—

The other patient was a 35 year old white female, treated in 1944 on the 250 kv. unit for an epidermoid carcinoma. She presented with unilateral enlarged neck lymph nodes, cranial nerve involvement, basal skull invasion and perforation of the soft palate by tumor. A depth dose of 6,600 r was delivered to the nasopharynx in 31 days. Three months later she received a second course for local recurrence; at this time, however, a considerably lower dose was given. In 1945 she was treated again, the radiation being directed primarily to the petrous apex, which was invaded. In 1948 she had another course of irradiation, directed to the nasopharynx for local recurrence again at that site. Due to radiation injury surgical resection of part of the mandible and later of the right mastoid process was necessary. She had persistent purulent drainage from the maxilla. She has required a gingivectomy, numerous tooth extractions along with adjacent alveolar bone repair, and an uvulectomy. The patient has survived 19 years and is clinically free of malignant disease. Her present complaint is of "fuzzy" vision, presumably due to radiation changes in the eye. None of our remaining 42 cases had been given a course of radiation therapy so vigorous as these 2 cases.

SUMMARY AND CONCLUSIONS

A series of 44 patients with malignant disease of the nasopharynx, treated at the New York Hospital—Cornell Medical Center from 1940 through 1958, is presented. Forty-two of these patients were treated by orthovoltage external roentgen therapy as the primary mode of treatment and 2 by a 1,000 c Co^{60} unit.

The over-all 5 year survival rate was 29.5 per cent. This is comparable to other series (Table vi). The time-dose approach to the primary lesion was similar in all cases. The chance of a 5 year survival is greatly increased when the patient, on

TABLE VI

FIVE YEAR SURVIVAL COMPARISONS

Series	No. of Patients	Per Cent 5 Year Survival
Present Series	44	29.5
Vaeth:[25] University of California Hospital, San Francisco, Calif.	82	28.2
Wang *et al.*:[26] Massachusetts General Hospital, Boston, Mass.	115	34.5
Martin and Blady: Memorial Hospital, New York, N. Y.	87	23.0
Kramer: Middlesex Hospital, London, England	55	15.0
Lenz:[14] Presbyterian and Montefiore Hospitals, New York, N. Y.	44	29.6
Nielsen:[19] Radium Center, Copenhagen, Denmark	77	14.3
Smedal and Watson: Lahey Clinic, Boston, Mass.	39	33.3

initial evaluation, has no evidence of enlarged neck lymph nodes, cranial nerve involvement, or local basal skull invasion. Histologically, lymphoepithelioma has the most favorable prognosis.

From this study, we are unable to draw a comparison between salvage rates of patients treated by supervoltage and orthovoltage methods. Only 2 cases were treated by cobalt 60 teletherapy (1 of the 2 survived 5 years and is clinically free of disease).

There were 2 instances of postradiation complications. Both patients had been overtreated.

Special emphasis is placed on the need for directing suspicion toward the nasopharynx in all patients presenting with cervical lymphadenopathy with or without accompanying hypoacusia or cranial nerve signs.

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MALIGNANT TUMORS OF THE NASOPHARYNX*

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THE aim of the authors is to elaborate upon the adaptation of radiation techniques to the anatomic routes of spread in patients with malignant tumors of the nasopharynx without previous treatment. All patients studied have had positive biopsy specimens from the nasopharynx.

Table I shows the histologic distribution of the 112 tumors found in previously untreated patients who were seen from 1948 through 1960. In this institution, the transitional cell carcinomas are included in the squamous cell carcinoma group, and the lymphoepitheliomas are considered a variant within the epithelial tumor group. In Table II, the distribution of the patients by age, sex, and race is given.

TABLE I

MALIGNANT TUMORS OF THE NASOPHARYNX
August, 1948–December, 1960

PATHOLOGY

	No. of Patients	Per Cent
Squamous cell carcinoma	53	47.3
Lymphoepithelioma	42	37.5
Unclassified	4	3.6
Primary malignant lymphoma	10	8.9
Plasmocytoma	1	0.9
Fibrosarcoma	1	0.9
Adenocarcinoma	1	0.9
Total	112	100.0

The anatomy of the nasopharynx and surrounding structures with the consequent lines of spread and natural history of the disease has been presented by Lenz[3] and Lederman.[2]

SPREAD TO CONTIGUOUS STRUCTURES

The nasopharynx is a small space enclosed by immobile contiguous structures, with the exception of the soft palate, the oropharynx, and the posterior nasal cavity. A submucosal growth may spread early to contiguous structures, or give rise to lymph node metastases and still be clinically undetectable in the nasopharynx.

Extensions along the posterior and lateral pharyngeal walls including the tonsillar area may be appraised by palpation. A history of sore throat should alert the examiner to search for oropharynx extension. Posterior pharyngeal wall extension can be clearly seen on lateral soft tissue roentgenograms. When the infiltration is posterolateral, it is a moot question as to whether one is dealing with an extension of the primary tumor or an enlarged parapharyngeal lymph node.

Extension through the posterior choanae into the nasal cavity must be carefully evaluated. When there is invasion of the posterior nasal fossae, possible invasion of the ethmoid cells should be investigated through careful laminagraphic studies of the paranasal sinuses. Occasionally, the maxillary antrum can be involved; this would be demonstrated on laminagrams of the paranasal sinuses.

The floor of the sphenoid sinus forms the roof of the nasopharynx and can, therefore, be involved very early. This involvement can be recognized on sagittal laminagrams by a break in the bony lining. A sclerotic reaction of the basisphenoid or the floor of the sphenoid sinus, seen either on the lateral roentgenogram or on the sagittal laminagrams, is not necessarily caused by involvement, but is strongly suggestive of

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TABLE II

MALIGNANT TUMORS OF THE NASOPHARYNX
August, 1948–December, 1960

AGE, SEX, AND RACE DISTRIBUTION

Age	Total	White		Negro		Latin American	
		Male	Female	Male	Female	Male	Female
14–19	9	4	4	—	—	1	—
20–29	7	3	2	2	—	—	—
30–39	10	9	1	—	—	—	—
40–49	22	17	3	2	—	—	—
50–59	29	20	5	4	—	—	—
60–69	20	11	5	3	—	1	—
70–79	14	7	4	2	1	—	—
80–89	1	1	—	—	—	—	—
Total	112	72	24	13	1	2	—

The youngest patient was 14 years of age, the oldest 81.

it. Several local recurrences noted on roentgenograms made before therapy could be, retrospectively, attributed to the presence of such sclerotic changes.

Bony invasion of the base of the skull is determined on the submental roentgenogram and coronal laminagrams. Spread to the cavernous sinus produces symptoms attributable to cranial nerve invasion. The sixth, fifth, fourth, and third cranial nerves are, in that order, the most commonly involved.[8,11] Invasion of the optic nerve results from parasellar invasion. In some of these cases, it is questionable whether the primary site is in the sphenoid sinus or in the nasopharynx. Involvement of the orbit has been rarely noted in the initial examination, but the orbit has been a site of recurrence in several instances. Invasion of the ninth, tenth, eleventh, and twelfth cranial nerves takes place in the parapharyngeal space by metastatic growth into the lymphatics.[2,3,6]

As shown in Table III, the incidence of spread to the base of the skull is about 25 per cent in the epithelial group, with no significant difference for the various types of epithelial tumors. This is higher than reported in most series, and is probably the result of extensive use of laminagraphy in the pretreatment examination. All patients except 1 with involvement of the base of the skull were subsequent failures. In no case did lymphoma invade the base of the skull or the cranial nerves. The incidence of spread to contiguous structures on admission is shown in Table IV.

SPREAD TO THE LYMPHATICS OF THE NECK

The malignant tumors of the nasopharynx are known to spread with high frequency to the neck lymph nodes, with variations in incidence from 70 to 90 per cent in reported series. The incidence in our series was 90 per cent (Table III).

The involvement is diffuse and often bilateral, even in the epithelial tumors (Fig. 1). In agreement with other series, the involvement of the deep upper jugular chain is most common. A deep lymph node palpable under the upper aspect of the sternocleidomastoid muscle is almost pathognomonic for a tumor of nasopharyngeal origin.

There is also a high percentage of involvement of the spinal accessory chain, the posterior cervical triangle, and the mid-jugular, lower jugular, and supraclavicular lymph nodes. On occasion, the only lymph nodes involved were mid- or lower jugular.

Table III

MALIGNANT TUMORS OF THE NASOPHARYNX
August, 1948–December, 1960

CLINICAL FEATURES ON ADMISSION

Histology	No Lymph Node Involvement		Unilateral Lymph Node Involvement		Bilateral Lymph Node Involvement		Lymph Node Involvement and Distant Metastases		Base of Skull Involvement		Cranial Nerve Involvement	
	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent
Squamous cell carcinoma (Grade I and II) 11 cases	3	27	5	46	3	27	—	—	1	9	1	9
Squamous cell carcinoma (Grade III and IV) 36 cases	3	8	13	36	19	53	1		10	28	5*	14
Squamous cell carcinoma (No grade) 6 cases	—	—	2	—	4	—	—	—	1	17	1	17
Lymphoepithelioma 42 cases	3	7	17	40	19	45	3	—	11	26	7†	17
Lymphoma 10 cases	4	—	4	—	2	—	—	—	—	—	—	—
Unclassified carcinoma 4 cases	—	—	1	—	3	—	—	—	2	50	1	25
Fibrosarcoma 1 case	1	—	—	—	—	—	—	—	—	—	—	—
Plasmocytoma 1 case	1	—	—	—	—	—	—	—	—	—	—	—
Adenocarcinoma of mucous gland 1 case	1	—	—	—	—	—	—	—	—	—	—	—
Entire group 112 cases	16	14	42	38	50	45	4‡	3.5	25	22	15	13
Epithelial group 99 cases	9	9	38	38	48	49	4‡	4	25	25	15	15

* All had base of skull involvement.

† Five of 7 had base of skull involvement.

‡ All 4 had clinical neck lymph node involvement.

In our material, submaxillary and submental lymph nodes have been involved rarely and only if there was massive involvement of the other lymph node areas.

A study of the relationship between histologic grading and lymph node metastases showed that the patients with lymphoepitheliomas and the more anaplastic squamous cell carcinomas had a slightly greater incidence of positive lymph nodes (92.5 per cent) than those with the more differentiated lesions (73 per cent).

ANATOMIC PLANNING

The anatomic treatment planning is the same for the various grades of squamous cell carcinomas, lymphoepitheliomas, and the lymphosarcomas, as there is no difference either in the patterns of spread to the contiguous structures or in the incidence and location of metastatic neck lymph nodes. The occasional plasmocytoma and cylindroma is studied on an individual basis; only the primary lesion is treated.

Ideally, one would like to include all potential areas of spread. The middle cranial fossa and perhaps the orbit, in addition to the nasopharynx, posterior nares, the parapharyngeal lymphatics, and all neck lymph nodes should be in the treatment field; however, large areas of the central nervous system would receive high doses of radiation. Although there have been recurrences within the cranial cavity, probably due to disease originally undetected, the risk of exposing all patients to central nervous system complications is not justified. In the patients studied, only 1 with initial cranial nerve or base of skull involvement has been salvaged.

Table IV

MALIGNANT TUMORS OF THE NASOPHARYNX
August, 1948–December, 1960

INCIDENCE OF SPREAD TO CONTIGUOUS STRUCTURES ON ADMISSION

Oropharyngeal wall	29
Base of skull (including sphenoid-11)	25
Tonsillar bed	15
Cranial nerves	12
Pterygoid fossa	9
Nasal cavity	5
Maxillary antrum	4
Orbit	3
Soft palate	3
Hard palate	2
Ethmoids	2
Hypopharynx	1

In several cases more than one structure was involved.

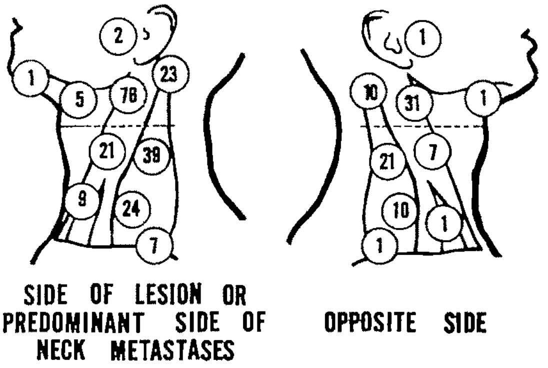

Fig. 1. *Distribution of metastases to various lymph node areas in epithelial tumors of the nasopharynx.* The encircled numbers indicate the number of times the particular lymph node is involved. Note the high incidence of involvement of the lymph nodes of the spinal accessory chain and midjugular and posterior cervical triangle, and—on the side predominantly involved by the lesion—a significant incidence of involvement of the low jugular and supraclavicular lymph nodes.

Total cases—99. No lymph nodes involved—10 (10 per cent); lymph nodes involved—89 (90 per cent); unilateral involvement—38 (39 per cent); bilateral involvement—51 (51 per cent).

The anatomic structures included in the portals covering the primary lesion are determined by the clinical or roentgenographic evidence of involvement of specific contiguous structures. When the disease is limited to the nasopharynx proper, most of the sphenoid sinus, the most posterior part of the nasal cavity and the posterior ethmoid cells are included in the treatment of the primary lesion. Known extensions beyond the nasopharynx are a valid reason for modification of geometry.

In continuity with the treatment of the primary lesion, the parapharyngeal lymphatics and all the lymphatics of the neck are irradiated, irrespective of whether there are palpable lymph nodes in any one of the lymphatic areas of the neck. The rationale for including lymphatic areas of the neck without palpable lymph nodes (with the exception of the submental and submaxillary areas, which are rarely involved) is that microscopic nests of cells are more readily controlled than are large tumor masses.

TUMOR DOSE

There is universal agreement that the tumor dose for the lymphosarcomas can be lower than that for the squamous cell carcinomas. Some authors[2] state that the lymphoepitheliomas belong to the lymphosarcoma group and should also be given lower tumor doses. In our material, local recurrences in the nasopharynx itself have developed in the lymphoepithelioma group treated with 6,000 rads or more. Some lymphoepitheliomas in neck lymph nodes have regressed extremely fast, others were not permanently controlled with 8,000 rads. This agrees with the concept that lymphoepithelioma is a variant of squamous cell carcinoma.[9]

Except for lymphosarcomas, a minimal tumor dose of 6,000 rads in 5½ to 6 weeks is the aim for the primary lesions. Since megavoltage has become available, at least 6,500 rads or even 7,000 rads are given when there are extensions to the base of the skull or cranial nerves. The reason for this is that tumor in bone or nerve sheath is more radioresistant. No less than 6,000 rads in 6 weeks, and sometimes up to 7,500 or 8,000 rads, are given to areas of the neck with palpable lymph nodes.

Although tumors which regress rapidly do not necessarily remain permanently controlled,[1] the regression rate is taken into consideration in adjusting the final dose for both the primary lesion and the neck lymph nodes. For instance, if by the fourth week there is no palpable tumor, it may be assumed that the basic dose of 6,000 rads will achieve control.

GEOMETRIC PLANNING

The lateral portals are first used to encompass most of the sphenoid, the nasopharynx, the parapharyngeal lymphatics, and the upper neck lymph nodes to the level of the thyroid notch. The submaxillary and submental areas are not included unless there are already large lymph nodes in the subdigastric areas (Fig. 2).

A tumor dose of 1,000 rads per week is well tolerated when megavoltage is utilized. A total dose of 4,000 rads is given through the lateral portals. As the neck is usually thinner than the head, the upper neck lymph nodes receive approximately 10 per cent more than the primary lesion.

The lower neck lymphatics are irradiated through an anterior split portal with a given dose of 1,000 rads per week (Fig. 3). As the midjugular, lower jugular, supraclavicular, and posterior cervical triangle lymph nodes are at the most 2 to 3 cm. below the skin, the dose to the lymph nodes varies from 100 per cent to 85 per cent of the given dose. For the lymphosarcomas, an additional 500 to 1,000 rads may be given to large neck masses and/or to the primary lesion, depending upon regression.

For epithelial tumors, if the disease is limited to the nasopharynx, 2 anterior portals, tilted medially and upward are used. A dose of 2,000 rads in 1½ to 2 weeks is delivered to the primary tumor in the nasopharynx. With the head in hyperextension, the lower split field is then raised until it is tangential to the angles of the jaw, thereby including the upper neck lymph nodes. An additional 1,000 rads are delivered to the upper neck, making the total dose to the lower neck 5,000 rads. If there are palpable lymph nodes in that area, 1,000 to 2,000 rads are given to a posterior split field or to small glancing fields.

If there is extension of the tumor to the oropharynx, the lateral portals are maintained, but they are reduced to include the nasopharynx and oropharynx only, the lower margin being at the angle of the jaw. If a 22 mev. betatron unit is available, it is used to deliver the last 2,000 rads, since it gives a more satisfactory volume distribution (Fig. 4). If a cobalt 60 unit is used, overdoses in the temporomandibular areas cannot be avoided.

If there is roentgenographic evidence of invasion of the sphenoid, the upper aspect of the portal is drawn to include the whole sinus. If there is roentgenographic evidence of invasion of the base of the skull, or clinical evidence of invasion of the cranial nerves, the 22 mev. betatron unit is used throughout therapy, and the fields include part of the ear in order to give more generous coverage of the middle cranial fossa (Fig. 2). The upper aspect of the lateral portal is then 2 to 3 cm. above the zygoma, the lower margin being at the angle of the jaw to include the parapharyngeal lymphatics. The final tumor dose is 6,500 or even 7,000 rads in 6 to 6½ weeks. The entire neck is then irradiated through anterior and posterior split portals.

When there is invasion of the nasal cavity, ethmoid cells, orbit, or paranasal sinus, the anterior portals are drawn from the eyebrow to the floor of the nose. Equal loading of the 4 fields may be used in order

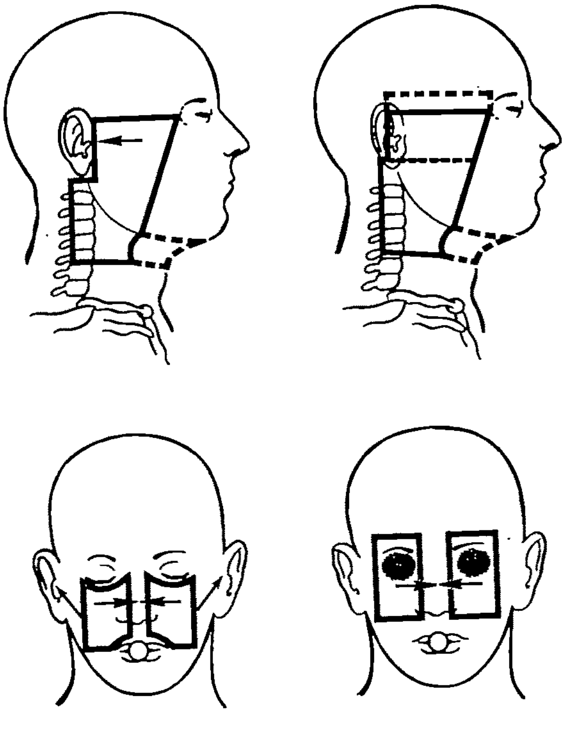

Fig. 2. *Portals for irradiation of primary tumor.*

Upper left: Lateral portal for a localized tumor. The ear is pulled backward and taped. The upper margin of the portal is drawn from the outer canthus to the upper margin of the tragus. The posterior margin is adjacent to the anterior aspect of the external auditory canal. The lower aspect of the portal is at the level of the thyroid notch. If there are palpable lymph nodes in the anterior subdigastric areas, the submental and submaxillary areas are included (dotted line). With the beam perpendicular to the skin surface, there is only marginal coverage of the slope and posterior wall of the nasopharynx. With a 5 degree tilt posteriorly, there is usually satisfactory coverage, and with a 10 degree tilt, part of the spinal cord may be in the beam. The tilt is determined by verification roentgenograms, varying from 5 to 10 degrees. This anatomic setup spares most of the skin of the ear, the external auditory canal, and the middle ear. It is to be preferred unless there is involvement of the base of the skull or cranial nerves.

Upper right: Lateral portal when there is invasion of the base of skull and/or cranial nerves. The upper margin (upper dotted line) of the lateral portal is drawn to include the sphenoid sinus, base of skull, and middle cranial fossa. The posterior aspect of the portal is back of the external auditory canal. The whole treatment is preferably given through lateral portals with the 22 mev. betatron unit. After 6,000 rads in 6 weeks, additional irradiation (500 to 1,000 rads) is given through reduced portals between the two dotted lines. If only a 2 to 6 mev. unit is available, it is preferable not to exceed a total dose of 5,000 rads through the lateral portals.

Lower left: Anterior portals for a localized tumor. The fields glance the eyeballs. There is a cork in the mouth. The portals are tilted medially (20 degree average) and the axis of the beam is aimed at the upper margin of the tragus which is the surface landmark of the slope of the nasopharynx.

Lower right: Anterior portals when there is involvement of the posterior nasal cavity, ethmoid cells, or orbit. One or both corneas are protected with a lead cylinder, provided disease is not shielded. The size of the anterior portals varies from 7×5 cm. to 9×7 cm., depending upon how much anterior coverage of the nasal cavity and ethmoid cells is indicated. The portals are drawn closer, with less medial tilt, when more anterior coverage is indicated.

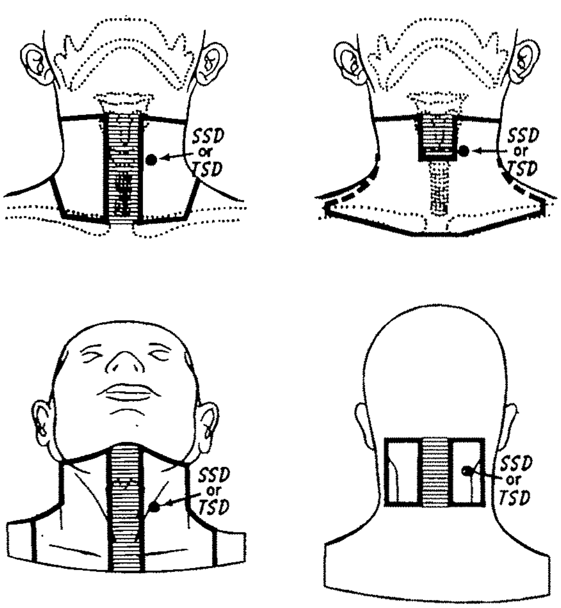

Fig. 3. *Portals for irradiation of lower neck lymphatics.*

There is a complete shielding of the midline (upper left) if there are no palpable lymph nodes in the lower neck. If there is disease in the lower neck, only the larynx is shielded and the posterior cervical triangle is covered entirely (upper right). The upper border of the lower neck field is raised (lower left) to include the upper jugular and subdigastric areas after 4,000 rads have been given to the primary lesion through lateral portals. A posterior split field (lower right) from the level of the mastoid to the midneck is used for additional treatment if upper neck lymph nodes are palpable. (SSD = source skin distance; TSD = target skin distance.)

to deliver a more generous dose to the ethmoid cells and nasal cavity. The cornea is protected on at least one side if there is no invasion of the orbits. A T-shaped arrangement, 2 lateral portals with wedge filter and 1 anterior portal, may occasionally be used.

Taking into consideration differential bone absorption, 5,000 to 5,500 rads are the maximum which can be given in 6 weeks with a 3 mm. Cu half value layer beam, whereas with megavoltage, up to 7,000 rads may be given in 6½ weeks.

With these techniques, the dose to the spinal cord is, at the most, 4,500 rads in 5½ to 6 weeks. In cases where there are extensions to the base of the skull or cranial nerves, part of the brain stem receives 6,000 rads or more.

With 1,000 rads per week employing megavoltage therapy, a fibrinous mucositis will usually develop during the second or third week. Special feeding formulas are helpful to maintain weight, but hospitalization is rarely necessary.

RESULTS OF TREATMENT

In several series,[2,3,6] the best survival rate was reported in patients with lymphoepithelioma. In fact, in some series the only survivors were patients with lymphoepithelioma.[6] Other series show a survival rate not too different for lymphoepithelioma and squamous cell carcinoma cases.[4,8,10,11]

In our material, the survival rates for patients with squamous cell carcinoma and lymphoepithelioma are not significantly different (Table v). Although fewer in number, the group of patients with lymphosarcoma have a higher survival rate. In Table vi is shown the survival rate for patients with epithelial tumors and unilateral or bilateral neck lymph node involvement. Again, there is no significant difference in survival rates between the patients with squamous cell carcinoma and those with lymphoepithelioma. One third of 43 patients with disease proved by biopsy of the neck prior to therapy are alive and free from disease at 5 years.

The factors influencing survival rates are summarized in Table vii. In cases of cranial nerve involvement, there were no survivors. In the group of patients with base of skull involvement, 2 survived 3 years and only 1 survived 5 years. In the 5 year survivor, a biopsy of the sphenoid sinus during an exploratory operation prior to radiation therapy was positive. The patient died from pulmonary metastases; there was no evidence of local recurrence.

The sites of failures in epithelial tumors are given in Table viii. The locations of local recurrences within contiguous struc-

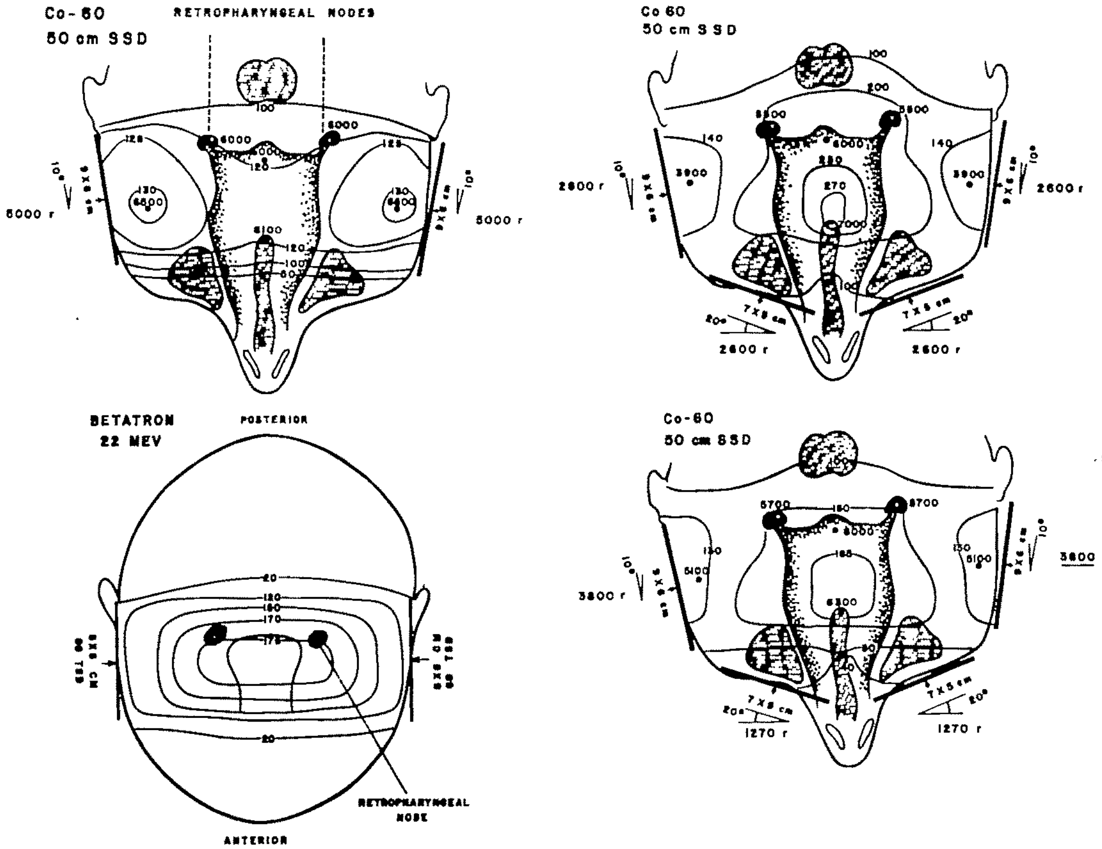

Fig. 4. *Dosimetry.*

Upper left: Dose distribution when the whole treatment is given through the lateral portals with cobalt 60. One can see that there is a higher dose in the temporomandibular areas than in the nasopharynx.

Lower left: Volume distribution for two lateral portals with a 22 mev. betatron unit.

Upper right: Dose distribution with equal loading to the 4 fields. This is a rule used in conjunction with the anterior portals shown in the lower right sketch in Figure 2, when there is involvement of the posterior nasal cavity and/or ethmoids.

Lower right: Dose distribution when a tumor dose of 5,000 rads has been given through the lateral portals. This pattern is used when there is extension to the oropharynx and/or palpable parapharyngeal lymph nodes are present. When the tumor is localized to the nasopharynx, 4,000 rads (tumor dose) is given through the lateral portals and 2,000 rads (tumor dose) through the portals shown in the lower left sketch in Figure 2. The given dose to each anterior portal is then approximately 1,600 to 1,800 rads.

tures are given in Table IX. Of the recurrences which developed locally or within contiguous structures, 86 per cent appeared within 2 years. In 1 patient, a lymphoepithelioma recurred locally 13 years after radiation therapy consisting of 5,000 rads to the nasopharynx. Local recurrences in the orbit, paranasal sinuses, and oropharynx are probably caused by failure to detect the initial extent of the tumor.

When those cases in which the disease was originally localized to the nasopharynx are compared, the differentiated squamous cell carcinomas show a somewhat higher rate of local failures than do the anaplastic carcinomas and the lymphoepitheliomas. It is possible that the well differentiated squamous cell carcinomas may require higher doses for complete regression and permanent control.[4,7,11]

In the kilovoltage series, there were 8 recurrences in patients who received around

TABLE V

MALIGNANT TUMORS OF THE NASOPHARYNX
August, 1948–December, 1960

RESULTS OF TREATMENT
ABSOLUTE AND DETERMINATE 5 AND 3 YEAR SURVIVORS

Survivor Group	Squamous Cell Carcinoma	Lympho-epithelioma	Unclassified Carcinoma	Adeno-carcinoma	Lymphoma	Plasmo-cytoma	Sarcoma	Total
Absolute* 5 Year Survival 1948–Dec., 1958	12/36 33%	14/35 40%	0/3	1/1	4/8 50%	1/1	0/1	32/85 38%
Determinate† 5 Year Survival	12/29 41%	14/31 45%	0/3	1/1	4/8 50%	1/1	0/1	32/74 43%
Absolute* 3 Year Survival 1948–Dec., 1960	24/53 45%	19/42 45%	1/4	1/1	6/10 60%	1/1	0/1	52/112 46%
Determinate† 3 Year Survival	24/47 51%	19/38 50%	1/4	1/1	6/10 60%	1/1	0/1	52/102 51%

* Absolute: Includes all cases of malignant nasopharyngeal disease registered, primary untreated at this hospital.

† Determinate: Excludes 1 patient not treated (died from cardiac failure immediately after admission), patients incompletely treated, and patients dying of intercurrent disease.

5,500 rads, and 4 recurrences in those who received less than 5,500 rads. In the megavoltage group, recurrences occurred in patients who received around 6,000 rads in 5½ to 6 weeks; there were no local failures in those patients who were given more than 6,500 rads.

Of 42 patients with lymphoepithelioma, there were 7 (16 per cent) in whom the neck disease was not controlled, while of 53 patients with squamous cell carcinoma, there were 11 (21 per cent) failures. The difference is not statistically significant. Recurrences were more common in patients with extensive bilateral lymph node involvement; although, there were 8 cures of 20 patients with small bilateral lymph nodes. The recurrences occurred mainly in the upper neck, especially in those patients with large masses in the subdigastric areas. Only 2 recurrences were found outside the irradiated area, 1 in the submental area,

TABLE VI

EPITHELIAL TUMORS OF THE NASOPHARYNX
August, 1948–December, 1960

ABSOLUTE 5 YEAR SURVIVAL ANALYZED BY REGIONAL LYMPH NODE INVOLVEMENT

Regional Spread	No. of Cases	Squamous Cell Carcinoma		Lympho-epithelioma		Unclassified Carcinoma		Absolute 5 Year Survival	
		Alive	Dead	Alive	Dead	Alive	Dead	No.	Per Cent
No lymph node involvement	7	1	4	1	1	—	—	2	29
Unilateral lymph node involvement	26	5	5	7	8	—	1	12	46
Bilateral lymph node involvement	37	6	14	6	9	—	2	12	32

The low survival rate in the 7 "no lymph node involvement" patients is without statistical significance. Of the 5 patients who died, 3 died from intercurrent disease. Four patients with both neck lymph node involvement and distant metastases on admission are not included in the table.

and the other in the suboccipital area. This incidence rate is too low to justify routine irradiation of these areas.

In a group of 40 patients in whom an incisional biopsy of lymph nodes had not been done, there were only 5 instances (12.5 per cent) of failure to control the neck disease. In 49 cases in which an incisional biopsy had been performed, there were 13 failures (26 per cent). Although there was a greater number of advanced cases in the group having incisional biopsy, it is possible that this procedure may have an unfavorable effect on the tumor bed and perhaps aspiration biopsy is to be preferred.

Neck dissections were performed in 6 patients for residual or recurrent disease in the lymph nodes. Two of the 6 patients are alive without tumor 4½ and 5½ years after irradiation. Both had uncomplicated wound healing after maximum neck doses of 6,000 rads and 7,000 rads, respectively.

Elective irradiation of the whole neck seems worthwhile. Of 98 patients treated for epithelial tumor, there were only 7 in whom the lower neck was not electively irradiated since, because of massive local disease or associated medical conditions, treatment was essentially palliative. There were no treatment failures attributed to a lymph node, not previously detected, in an electively irradiated area, where the primary and palpable neck lymph nodes had been controlled.

Table VII

MALIGNANT TUMORS OF THE NASOPHARYNX
August, 1948–December, 1960

SUMMARY OF FACTORS INFLUENCING 5 YEAR SURVIVAL

	No. of Cases	Absolute 5 Year Survival
Cervical lymphadenopathy (epithelial only)		
No lymph node involvement	7	29%
Unilateral lymph node involvement	26	46%
Bilateral lymph node involvement	37	32%
Distant metastases (epithelial)	4	0
Invasion of base of skull (epithelial)	25/99	1 case*
Cranial nerve involvement (epithelial)	15/99	0
Pathology		
Squamous cell carcinoma	12/36	33%
Lymphoepithelioma	14/35	40%
Lymphoma	4/8	50%

* Dead at 6½ years from distant metastases.

Table VIII

EPITHELIAL TUMORS OF THE NASOPHARYNX*
August, 1948–December, 1960

CAUSES AND SITES OF FAILURE IN 98 CASES
(Unlimited Follow-up Time†)

No data	8
Primary lesion uncontrolled	10
Neck lymph node involvement uncontrolled	2
Distant metastases	16
Primary lesion plus neck lymph node involvement uncontrolled	7
Primary lesion and neck lymph node involvement uncontrolled plus distant metastases	3
Primary lesion uncontrolled plus distant metastases	4
Neck lymph node involvement uncontrolled plus distant metastases	6
Intercurrent disease	15
Complications of radiation treatment	3

* Excluding 1 untreated case.
† Many of these patients lived over 5 years.

DISTANT METASTASES

Distant metastases were the sole cause of failure in 16 patients; however, a total of 29 patients developed distant metastases alone or concomitantly with recurrence. Distant metastases as the sole or associated cause of failure were seen more often in the lymphoepithelioma group than in the squamous cell carcinoma cases. Of the lymphoepithelioma patients, 38 per cent developed distant metastases and in 24 per cent, it was the only known cause of failure.

COMPLICATIONS

MINOR COMPLICATIONS

Dental caries is an almost unavoidable sequela. Only 2 patients have retained noncarious teeth, 1 for 8 years and 1 for 6 years.

TABLE IX

MALIGNANT TUMORS OF THE NASOPHARYNX
August, 1948–December, 1960

SITES OF LOCAL RECURRENCE*

Nasopharynx	17
Base of skull	12
Brain	5
Cranial nerves	7
Orbit	3
Paranasal sinus	5
Nasal cavity	4
Lacrimal sac	1
Oropharynx	2
Mastoid, Middle ear	1

* Includes all histologic varieties. Several patients had a local recurrence in more than one anatomic location.

TABLE X

MALIGNANT TUMORS OF THE NASOPHARYNX
August, 1948–December, 1960

MAJOR COMPLICATIONS

	No. of Cases	No. of Fatalities
Radiation myelitis	4	3
Maxilla, necrosis-persistent	1	
Contracture of nasopharynx with 9th, 10th, 11th and 12th nerve paralysis	1	
Rupture of common carotid artery after radical neck dissection for recurrence	1	1
	7	4

Full mouth extraction before irradiation is advised for patients with poor teeth for whom curative therapy is planned; for those with healthy teeth, removal of the teeth in the direct pathway of radiation (*i.e.*, molars) is advisable. If palliative therapy only is indicated and the patient has a short life expectancy, the teeth should not be removed.

Otitis media was recorded in 7 cases; partial intermittent deafness occurred, but in no instance was deafness complete or a handicap. Minor necroses of the nasopharynx, mandible, or nasal septum healed with conservative treatment.

MAJOR COMPLICATIONS

Seven major complications are listed in Table x. Four authenticated cases of radiation myelitis have been observed; 3 were fatal and 1 was self-limiting. One patient had received an estimated 6,500 rads in 8 weeks and another an estimated 5,600 rads in 6 weeks to the brain stem. The patient with the self-limiting myelitis had received 6,000 rads tumor dose in 36 days to the nasopharynx. Myelitis can probably be avoided by not exceeding 5,000 rads to the brain stem and cervical cord in not less than 5 weeks.

The only patient treated with the cobalt 60 rotational technique developed stenosis of the nasopharynx requiring daily dilatation at home with a rubber catheter; he has also developed unilateral paralysis of the ninth, tenth, eleventh, and twelfth cranial nerves, probably secondary to fibrosis in the parapharyngeal area. This patient is free of disease 8 years after therapy.

SUMMARY

Radical comprehensive radiation therapy of both the primary lesion and neck lymph nodes yielded a survival rate of 35 to 40 per cent in patients with malignant tumors of the nasopharynx. The survival rates do not vary significantly for the various histologic categories of the disease.

A significant number of patients with neck lymph node metastases, even bilateral, have been salvaged. Invasion of the base of the skull and/or cranial nerves carries a fatal prognosis.

The geometric plan must be adapted when extensions of the disease are present. The final tumor dose is determined by the tumor bed (bone, cartilage, nerve sheaths) and the size of the masses. No consideration is given to the histologic type except in the case of lymphosarcoma.

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DOSE-TIME RELATIONSHIPS IN CANCER RADIOTHERAPY*

A CLINICAL RADIOBIOLOGY STUDY OF EXTREMES OF DOSE AND TIME

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A GIVEN dose of ionizing radiations is less effective in x-ray and gamma-ray human cancer radiotherapy when administered in fractions over a period of days than when administered in a single short session. Conversely, the total dose of fractionated irradiation administered over a period of days must be greater, for the induction of equal human cancericidal and other radiation effects, than that dose which induces these effects in a single short session. This reciprocal relationship of the parameters, radiation dose, dose fractionation, and over-all time is given the name dose-time relationship. It has been studied, both casually and systematically, since the discovery of the x-rays in 1895.

Despite a certain degree of continuous preoccupation with this relationship there are, as yet, no generally acceptable optimal parameters for it in human cancer radiotherapy. There are many administrative reasons for delivering the total dose of radiation in a single short session: patient visits and setting-up times would be limited to the absolute minimum, the use of radiation-producing facilities would be more efficient, relatively more time could be spent in essential preliminary treatment planning, and relatively less time would be spent in merely repetitive operations. Nevertheless, it is standard contemporary practice to employ some variety of fractionated dose and extended time or protraction pattern in human cancer radiotherapy. There are two reasons why this obtains. The one, given the name radiation sickness, is single dose limiting; the other rests upon the assumption of differential responses in the cancericidal and normal tissues radiation effects related to fractionation and protraction. It is probable that radiation sickness can be controlled by appropriate medical therapy. It is one of the purposes of this communication to examine the validity of the assumption and the nature of differential radiation responses related to dose-time factors. In examining this assumption and the changing concepts surrounding it, I shall review certain historical aspects of the development of the dose-time concept and the radiobiological theory and experiments which are resulting in the changing ideas concerning it and I shall report and discuss the clinical observations and results of radiotherapy in 2 selected groups of patients with cancer of the upper food and air passages treated by external beam radiotherapy at extremes of dose and time.

HISTORICAL AND RADIOBIOLOGICAL DEVELOPMENT

Because of a personal, long-time interest in the dose-time relationship in radiotherapy,[4–8] I undertook the clinical study which I am reporting herein on June 11, 1955. The concepts upon which this study was undertaken do not necessarily obtain today because of the rapid development of mammalian cell radiobiology; I shall, therefore, discuss the clinical studies on the bases of those concepts which do obtain today. The first studies in mammalian cell radiobiology quantitatively relating cell reproductive capacity or cell survival and radiation dose were reported only in 1956.[89] But 25 years earlier,[20] in presupervoltage days, a concept of high-dose, hyper-fractionation, and hyper-protraction was introduced into clinical radiotherapy practice. This, in turn, was based upon certain antecedent radiobiological observations reported in 1927[40] which were interpreted as showing that differential radiosensitivity of the testis in respect to that of the skin was increased by dose fractionation. This interpretation was largely based upon concepts of radiosensitivity which were elaborated very soon (1906)[12] after the discovery of the x-rays, concepts which, while not necessarily valid, are still widely held today. Inasmuch as these concepts affect the interpretations which may be put upon the findings of modern mammalian cell radiobiology and upon some of the clinical observations to be reported herein, I attempted, in 1962,[2] a redefinition of the phenomenon of radiosensitivity. A general conclusion of this redefinition was that there is a radiosensitivity component which I defined as inherent radiosensitivity and which is dependent upon cell properties, *per se*, and which is distinct from a second component which I defined as apparent radiosensitivity and which is dependent upon the irradiation conditions. Further, in another study[3] I have concluded that there are probably but small, if any, differences in the inherent radiosensitivities of the cells of the cancerous or the normal tissues of a given mammalian species. In a somewhat neglected study reported in 1925,[1] the results of experiments were cited which showed, in a dividing cell population biological test object, that radiation injury* must be interpreted from the points of view of both the immediately induced radiation lesion and the postradiation manifestation of this lesion. It was concluded that the postradiation manifestation of the radiation lesion was a function of both the biological stresses inherent in the test object and the postradiation conditions to which the test object was exposed and that the biological stress which was largely determinative of the postradiation manifestation of the radiation lesion was the necessity for cell division. In those tissues where this stress is great, lethal injury of cell reproductive capacity would be quickly manifest; in those tissues where it is absent or slight, there might be no demonstrable or only very late demonstrable effects. Representative tissues in the human are the hemopoietic and nervous. It was emphasized that such differences did not imply a differential radiosensitivity in respect to the induction of the initial radiation lesion; radiosensitivities could be equal; only the development of the postradiation manifestations might be different.

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My own studies of the dose-time relationship have been much influenced by the first real attempt, in 1954,[49] in clinical cancer radiotherapy at a quantitative systematization of this relationship. On the bases of this systematization and other relationships which I developed, I showed, in 1957,[6] that the capacity for recovery in fractionated and protracted clinical cancer radiotherapy could be evaluated quantitatively in terms of the difference between the total radiation dose given in fractional increments over a period of time and the single dose which produced the radiation effect, the "recovery fraction." In 1958[7] I defined the limit of tolerance as 10,000 r for multi-fractionated (43 equal fractions) and very protracted (100 days) radiotherapy of cancer of the upper food and air passages. In 1959[22] the kinetics of postradiation cellular recovery were elucidated. It was suggested in 1960[27] that the exponent, n, of the dose-time equation, $D=kt^n$,† appeared to

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* I shall employ certain terms, radiation injury, recovery, repair, and restitution, to which I have assigned the following special meanings:

Radiation injury—cellular radiation effects which may be either: lethal—resulting in the loss of unlimited cell reproductive capacity and the subsequent death of either the irradiated cell or its progeny, or sub-lethal—from which recovery will be effected.

Recovery—restoration, after sub-lethal radiation injury, of pre-irradiation parameters of cellular reproduction and radiation response.

Repair—cellular repopulation of tumor or normal tissue after recovery from injury.

Restitution—recovery and repair.

† Where D is the total dose administered in multiple increments in t time, k is a constant having the value of the single dose for the specific response, t is the time in days over which the total dose, D, is administered, and n is a positive fraction,

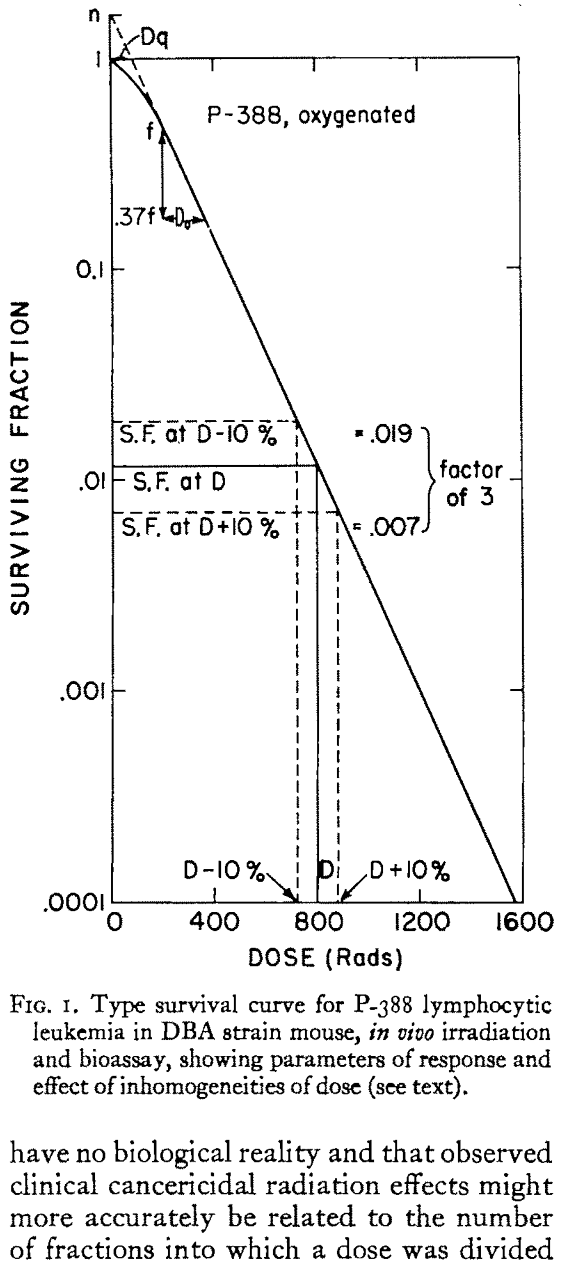

Fig. 1. Type survival curve for P-388 lymphocytic leukemia in DBA strain mouse, *in vivo* irradiation and bioassay, showing parameters of response and effect of inhomogeneities of dose (see text).

have no biological reality and that observed clinical cancericidal radiation effects might more accurately be related to the number of fractions into which a dose was divided than to the over-all time in which it was administered. This view has only limited validity, however, for the time between fractional increments of dose is very important in respect to cell restitution processes; if this time is long in relation to the cell population doubling time of the irradiated cancer, progressive de-population of it may not occur; if it is short in relation to normal repair processes, normal cell populations may be depleted.

Certain of the parameters of the response of a cell population to irradiation may be displayed as a survival curve relating logarithmically the fraction of irradiated cells retaining their reproductive capacity, or surviving fraction, to radiation dose. Commencing, in 1961, with the published work of Berry and Andrews,[14] such parameters of response have been studied by a number of investigators[9,10,11,15,16] in our laboratories under a variety of irradiation conditions which influence both apparent and inherent radiosensitivity. A typical survival curve for the P-388 lymphocytic leukemia growing in the DBA mouse and irradiated under oxygenated conditions is shown in Figure 1. The survival curve may be characterized in the straight line (exponential) portion of the curve by D_0, the dose required to reduce a surviving fraction to 37 per cent of this fraction, and by n and D_q, the number on the vertical coordinate and the dose, respectively, to which the exponential portion of the survival curve extrapolates.

An ingenious analysis, in 1963,[28] of the parameter, D_q, of survival curves of the general type of Figure 1 showed that this parameter could be determined by comparing, in dose fractionation experiments, the total fractionated dose with the single dose required for the equivalent effect and, where each fractional dose is large enough to displace the surviving fraction to the exponential region of the survival curve, that:

$$D_q = \frac{D_f - D_1}{f - 1},$$

where D_f is the total dose administered in f fractions, D_1 is the single dose required for the equivalent effect, and $f-1$ is the number of intervals between the fractional dose increments. No account is taken of the time between the fractional dose increments for it is assumed that during the total irradiation period there have been no changes in the irradiated cell population aside from those induced by the irradiation itself and that recovery from sublethal injury is effected between fractions. The quantity, $D_f - D_1$ will be recognized as that which I termed the recovery fraction in 1957[6] and the parameter, D_q, may also be found by dividing this recovery fraction by the number of intervals between fractions. In a very careful study reported in 1947,[31] it was shown that the curative single exposure for small cancers of epidermal origin was 2,700 r and for multiple fractions administered in 1 week the curative exposure was 4,500 r. The actual number of fractions was not stated in the report but if it were 6, D_q, when calculated as shown above, has the value of 360 r. The number of tumor cells per unit mass of human cancer of epidermal origin has not been determined, but, if it is of the order of 10^8/gm., it may be presumed that the small cancers reported in this study contained between 10^7 and 10^8 reproductively intact cells. On the bases of these and the preceding considerations, the survival curves of Figure 2 have been constructed,* and it is considered that these represent descriptions, acceptable for the purposes of this presentation, of the radiation responses of human cell populations. As the curves are constructed, they become exponential at the 10 per cent level of the surviving fraction but perhaps they may

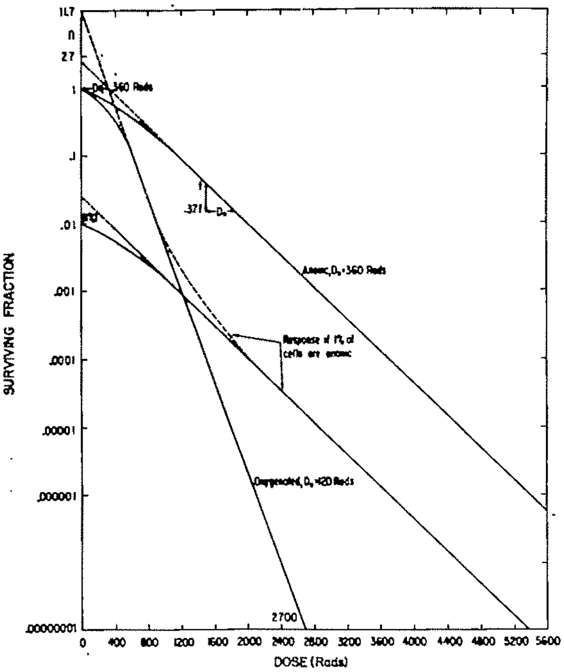

FIG. 2. Proposed survival curves for human cells. See text for derivation of parameters of response.

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* Substituting the exposures cited above, 2,700 r single and 4,500 r multiple (6, say, equal fractions), in the equation:

$$D_q = \frac{D_f - D_1}{f - 1}$$

$$= \frac{4500 - 2700}{6 - 1}$$

$$= 360 \text{ r.}$$

This defines the dose to which the exponential portion of the cell survival curve extrapolates. The surviving fraction .00000001, at 2,700 rads may be considered to be the probability of the survival of 1 of a population of 10^8 cells of a fully oxygenated population. A straight line drawn between the points so derived is the exponential portion, and its extrapolation of the survival curve and n is found by extending the extrapolation to the zero dose coordinate. D_0 is determined graphically. The curvilinear portions of the survival curves of Figure 2 are drawn freehand to their origins from the 10 per cent surviving fraction levels.

Radiosensitivity is defined in reference to the slope, to which D_0 is inversely related, of the exponential portion of the survival curve and is given the value of the reciprocal of its D_0. The radiosensitivity of a fully oxygenated population of cells is not likely to be greater than that of a wholly anoxic population by more than a factor of 3 so that if:

$$\frac{\text{radiosensitivity (oxygenated)}}{\text{radiosensitivity (anoxic)}} = 3$$

and

$$\text{radiosensitivity} = \frac{1}{D_0},$$

then

$$\frac{\frac{1}{D_0}\text{(oxygenated)}}{\frac{1}{D_0}\text{(anoxic)}} = 3 = \frac{\frac{1}{120}}{\frac{1}{D_0}\text{(anoxic)}}$$

and

$$D_0 \text{ (anoxic)} = 360 \text{ r}$$

for the condition of least radiosensitivity due to the oxygen effect.

As D_q is fixed, the values of n for the oxygenated and anoxic survival curves will be different.

There is, obviously, a high degree of artificiality in the manipulation of numbers in this manner. If, however, mammalian cell survival curve theory is to play a role in the development of concepts of clinical radiotherapy, then such points of departure must be taken despite the fact that data permitting the establishment of absolute parameters of human cell radiation responses are not presently available. These survival curves, as developed, are, simply, points of departure for the clinical concepts developed herein.

become exponential even as high as the 50 per cent level. Where appropriate, it is these curves which will be referred to in the clinical report which follows.

CLINICAL STUDY

The purpose of the clinical study is to present the clinical observations of the effects of radiotherapy administered under certain conditions of dose and time and to relate these effects to the theoretical considerations and the experimental findings of contemporary mammalian cell radiobiology. The case material is comprised of 2 groups of patients with epithelial cancer of the head and neck. One group, Series I, of 43 patients was irradiated with modal exposures of 9,000 r, administered as a modal number of 43 fractions of 210 r each over periods of about 100 days; the other group, Series II, of 20 patients was irradiated with single exposures of 2,000 (5 patients), 2,500 (14 patients), or 2,750 (1 patient) r. The clinical observations reported here carry, in themselves, no implications for the evolution of an optimal relationship of dose and time, but, when they are interpreted within the framework of contemporary cell radiobiology, they suggest certain conclusions concerning such an optimal relationship.

The importance which attaches to prospects for the evolution of an optimal relationship of dose and time has been given formal acknowledgement by the formation of a "Working Party on the Effects of Dose Fractionation in Radiotherapy" by the British Institute of Radiology.[21,38]

The clinical characteristics of the case material are presented in Table I where they are described in terms of the clinical diagnoses, the extent of disease according to the T.N.M. classification of the International Union Against Cancer, as shown in Table II, and the treatment. The histopathological diagnosis was in all instances epithelial cancer (squamous cell carcinoma). All of the patients included in this work were admitted for study and general care to the clinical service of the Radiation Branch, National Cancer Institute, which also planned and administered the radiotherapy. The limited availability of appropriate cases to the Radiation Branch provided no opportunity for randomization either within or between groups and the two groups; Series I, high dose-prolonged time, and Series II, single dose, were studied and irradiated sequentially, not simultaneously. The complications and late reactions of the radiotherapy are presented in Table III. The year of treatment and the survival times of individual cases after the start of treatment are shown in Table IV.

DOSIMETRY

In the irradiation of these two series of cases, it has been the practice to quantify the radiation in terms of roentgens (r) of exposure (X) rather than in terms of rads of absorbed dose (D).* The implications of the two units in respect to the quantification of radiation are recognized and such conversion factors may be applied to the exposures tabulated as are appropriate to the irradiation modality, 2 mev. Van de Graaff, employed. Quantification has been maintained in round numbers of r. Over-all treatment time (*t*) is expressed in days and fractionation (*f*) has been constant in the Series I cases with equal increments of exposure having been given thrice weekly. Irradiation was performed in most instances through two fields of mean sizes 10×7 and 9×7 cm.

Insofar as it has been possible and within the limits of the preceding, the dosimetry recommendations of the Faculty of Radiologists[48] have been followed. The exposures cited in Table I are considered to be the individual modal tumor exposures. Maximum and minimum tumor exposures did not

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* Radiation units as recommended by the International Commission on Radiological Units and Measurements (ICRU), NBS Handbook 84, Radiation Quantities and Units, GPO, 1962:

Term	*Symbol*	*Unit*
Absorbed dose	D	rad
Absorbed dose rate		rad s^{-1}
Exposure	X	R (roentgen)
Exposure rate		R s^{-1}

differ from the modal by more than 10 per cent. The importance, in terms of the surviving fractions of irradiated cell populations, of deviations from the modal exposure is illustrated by a consideration of Figure 1. At high increments of dose, not only does a given per cent deviation represent a relatively large value of exposure but

Table I

IDENTIFICATION, DIAGNOSIS, EXTENT OF DISEASE AND DETAILS OF RADIOTHERAPY

Serial No.	NIH No.	Sex	Age	Primary Site	Extent of Disease (Table II) Primary	Extent of Disease (Table II) Lymph Nodes	Exposure (r)	Fractions (No.)	Time (days)
				SERIES I					
1	01–07–63	M	52	Oropharynx	T_4	N_2	8,000	44	100
2	00–02–63	M	72	Base of Tongue	T_3	N_0	8,000	44	100
3	01–16–32	F	70	Antrum	T_4	N_0	10,000	43	98
4	01–07–78	M	8	Antrum	T_4	N_3	8,000	45	100
5	01–20–83	F	59	Oropharynx	T_4	N_2	10,000	43	96
6	01–24–05	M	67	Hypopharynx	T_3	N_1	9,530	82	93
7	01–27–60	M	35	Tonsil	T_2	N_1	10,000	43	98
8	01–31–23	M	86	Anterior Tongue	T_3	N_1	10,000	44	100
9	01–30–16	M	75	Anterior Tongue	T_3	N_3	7,788	34	80
10	01–47–22	M	71	Antrum	T_3	N_0	8,058	130	86
11	01–47–91	F	28	Nasopharynx	T_2	N_3	8,000	82	86
12	01–53–06	M	71	Base of Tongue	T_2	N_1	8,000	34	85
13	01–08–99	M	14	Nasopharynx	T_3	N_2	7,700	44	100
14	01–62–32	M	80	Hypopharynx	T_1	N_1	8,000	36	100
15	01–70–95	M	43	Nasopharynx	T_1	N_0	8,000	58	99
16	01–73–20	M	49	Hypopharynx	T_1	N_2	8,000	43	100
17	01–73–69	M	75	Palate	T_2	N_0	9,600	43	99
18	01–85–06	F	32	Nasopharynx	T_3	N_1	9,100	42	96
19	01–83–82	M	68	Larynx	T_3	N_0	9,000	47	99
20	01–86–45	M	69	Hypopharynx	T_3	N_3	8,200	37	88
21	01–83–92	M	62	Palate	T_3	N_3	7,080	38	74
22	01–89–34	M	49	Base of Tongue	T_3	N_1	9,000	42	99
23	01–86–34	F	62	Palate and Antrum	T_3	N_0	7,150	33	92
24	01–85–97	M	72	Oropharynx	T_3	N_3	9,000	44	103
25	01–07–27	F	59	Supraglottis	T_2	N_0	8,500	40	98
26	00–78–67	M	14	Nasopharynx	T_2	N_3	8,500	46	100
27	00–82–61	M	53	Nasopharynx	T_3	N_3	8,000	54	100
28	00–88–98	M	49	Base of Tongue	T_2	N_3	9,000	42	100
29	00–91–20	M	59	Supraglottis and Tonsil	T_2	N_3	9,000	43	99
30	00–96–26	M	29	Cheek	T_4	N_3	9,000	42	98
31	02–05–46	M	87	Supraglottis	T_3	N_0	9,000	43	99
32	02–06–88	F	67	Tonsil	T_1	N_2	9,000	42	100
33	02–06–37	M	72	Supraglottis	T_2	N_3	7,700	58	105
34	02–14–61	M	72	Tonsil	T_2	N_3	9,000	65	100
35	02–16–62	M	69	Larynx	T_3	N_0	9,000	43	103
36	02–21–40	M	49	Glottis	T_1	N_0	10,000	43	100
37	02–27–53	M	57	Tonsil	T_3	N_3	9,000	43	101
38	02–23–84	M	80	Tonsil	T_2	N_3	9,000	43	99
39	02–40–27	M	32	Glottis	T_2	N_1	9,000	43	98
40	02–55–52	M	58	Oropharynx	T_2	N_2	9,000	43	99
41	02–59–10	M	49	Glottis	T_1	N_0	9,000	43	97
42	02–62–26	M	69	Glottis	T_2	N_0	9,004	43	99
43	02–66–06	F	71	Floor of Mouth	T_3	N_0	8,545	41	94

TABLE I (*Continued*)

Serial No.	NIH No.	Sex	Age	Primary Site	Extent of Disease (Table II) Primary	Extent of Disease (Table II) Lymph Nodes	Exposure (r)	Fractions (No.)	Time (days)
				SERIES II					
1	02-88-01	F	67	Buccal Mucosa	T_2	N_0	2,500	1	1
2	02-97-72	F	71	Buccal Mucosa	T_3	N_0	2,000	1	1
3	03-14-97	F	48	Supraglottis	T_3	N_3	2,500	1	1
4	03-17-20	F	42	Nasopharynx	T_1	N_0	2,500	1	1
5	03-12-55	M	72	Retromolar	T_1	N_0	2,500	1	1
6	03-36-11	F	57	Base of Tongue	T_2	N_0	2,500	1	1
7	03-38-66	M	60	Oropharynx	T_3	N_0	2,500	1	1
8	03-48-86	M	56	Glottis	T_2	N_0	2,500	1	1
9	01-40-05	M	58	Supraglottis	T_2	N_0	2,500	1	1
10	03-65-56	M	53	Anterior Tongue	T_3	N_0	2,750	1	1
11	03-72-85	M	70	Palate	T_3	N_0	2,500	1	1
12	04-05-07	M	58	Hypopharynx	T_2	N_0	2,000	1	1
13	04-03-16	F	42	Tonsil	T_3	N_3	2,500	1	1
14	04-09-09	M	53	Tonsil	T_2	N_0	2,500	1	1
15	04-11-32	M	48	Hypopharynx	T_3	N_1	2,500	1	1
16	04-18-61	F	53	Tonsil	T_2	N_0	2,000	1	1
17	04-17-98	M	59	Hypopharynx	T_3	N_3	2,500	1	1
18	04-19-39	M	49	Glottis	T_1	N_0	2,500	1	1
19	04-35-51	M	47	Palate and Antrum	T_3	N_0	2,000	1	1
20	04-48-78	F	43	Tonsil	T_3	N_3	2,000	1	1

surviving fractions of the cell population between regions of low and of high dose may differ by as much as a factor of 3, as shown in the figure. Both the absolute differences of exposure, for a given per cent deviation from the modal, and of surviving fractions will be much lower when the increments of dose are small. Such considerations have a bearing on the problem of the evolution of optimal dose and time relationships. The exposure of the enveloping tissues (skin) was, in most instances, substantially less than the tumor modal exposure and in no instance was it greater; that of the lining tissues (mucous membranes) is considered to have been equal to or, at isolated points, greater than the tumor modal exposure; and that of the intervening supporting (bone, cartilage, connective tissue) and sustaining (blood and lymph vessels, nervous tissue, salivary glands) tissues was greater in some and less in other instances than the tumor modal exposure. In some instances, one or the other of lead wedge or fully compensating lucite filters or both were employed, each being placed at a minimum distance of 30 cm. from the skin. The target-skin or target-tumor distances varied between 80 and 125 cm. and the tumor exposure rate between 0.66 and 1.2 r s^{-1}.

TABLE II

T.N.M. CLASSIFICATION, INTERNATIONAL UNION AGAINST CANCER

T_1	Primary less than 3 cm. in size
T_2	Primary 3–5 cm. in size
T_3	Primary greater than 5 cm. with limited extension
T_4	Massive
N_0	Regional lymph node metastases not mentioned or none present
N_1	Lymph node single <3 cm. or two adjacent <2 cm. each
N_2	Single >3 cm., movable or multiple unilateral
N_3	Single >3 cm., fixed or bilateral
M	Distant metastases

GENERAL CONSIDERATIONS

Human cell populations may be characterized, within limits, by the kinetics of changes in these populations. Non-steady-state proliferating cell populations exist normally in embryonic, growing, and regenerating tissues and abnormally in cancer tissues; steady-state cell renewal, cell removal populations are characteristic of the normal adult; non-steady-state decreasing cell populations occur as a result of the aging process, ionizing radiations, and other injury. In both steady-state and non-steady-state systems, there is a constant turning over of cells with, in the one case, a balance between cell renewal and cell removal and, in the other, an imbalance. This relationship may be given the form of two continuous functions of the rates of cell renewal, $F(t)$, and cell removal, $G(t)$ and where M is the cell population number at a moment t, then:[23]

$$M = \int_0^t F(t)dt - \int_0^t G(t)dt.$$

If both $F(t)$ and $G(t)$ are exponential functions then M will also be an exponential function and, indeed, the growth of many human tumors appears to be exponential.[19,29,47] In normal tissue steady-state cell renewal, cell removal systems, the $F(t)$ and the $G(t)$ functions are in states of dynamic equilibrium and M is a constant. The time required for these renewal and removal phenomena to occur in a population of cells is given the name cell population turnover time. The time required for the cells of a non-steady-state proliferative cell population to double their number is given the name, in cancer, cell population doubling time. Homeostatic regulators or homeostatic regulatory mechanisms are involved in the control of these cell population dynamic phenomena but their role in the radiation responses of these phenomena is not known at this time and, for the present, it seems better to attempt an explanation of radiation responses on the bases of the direct radiation effects on cell populations.

Table III

RADIATION COMPLICATIONS

Complication	Series I (43 Cases)	Series II (20 Cases)
Skin: Ulceration	0	0
Mucous membrane		
Mucositis, severe	0	7
Ulceration	3	8
Fistula	1	0
Salivary glands	See text	
Soft tissues		
Fibrosis, marked	2	0
Necrosis and hemorrhage	4	2
Laryngeal		
Edema	1	4
Hoarseness	0	2
Cartilage necrosis	0	2
Tracheostomy	1	4
Pharyngeal		
Dysphagia and cachexia	1	7
Pharyngostomy or gastrostomy	0	2
Bone		
Alveolar necrosis	0	2
Articular		
Trismus	5	3
Middle ear deafness	2	2
Nervous system		
Neuritis requiring section	1	0
Encephalopathy	1	0

The cell population turnover time of human epithelium is very short compared with the cell population doubling times of human cancers of epithelial origin.* Where such a differential exists in the dynamics of the normal and cancer cell populations, suit-

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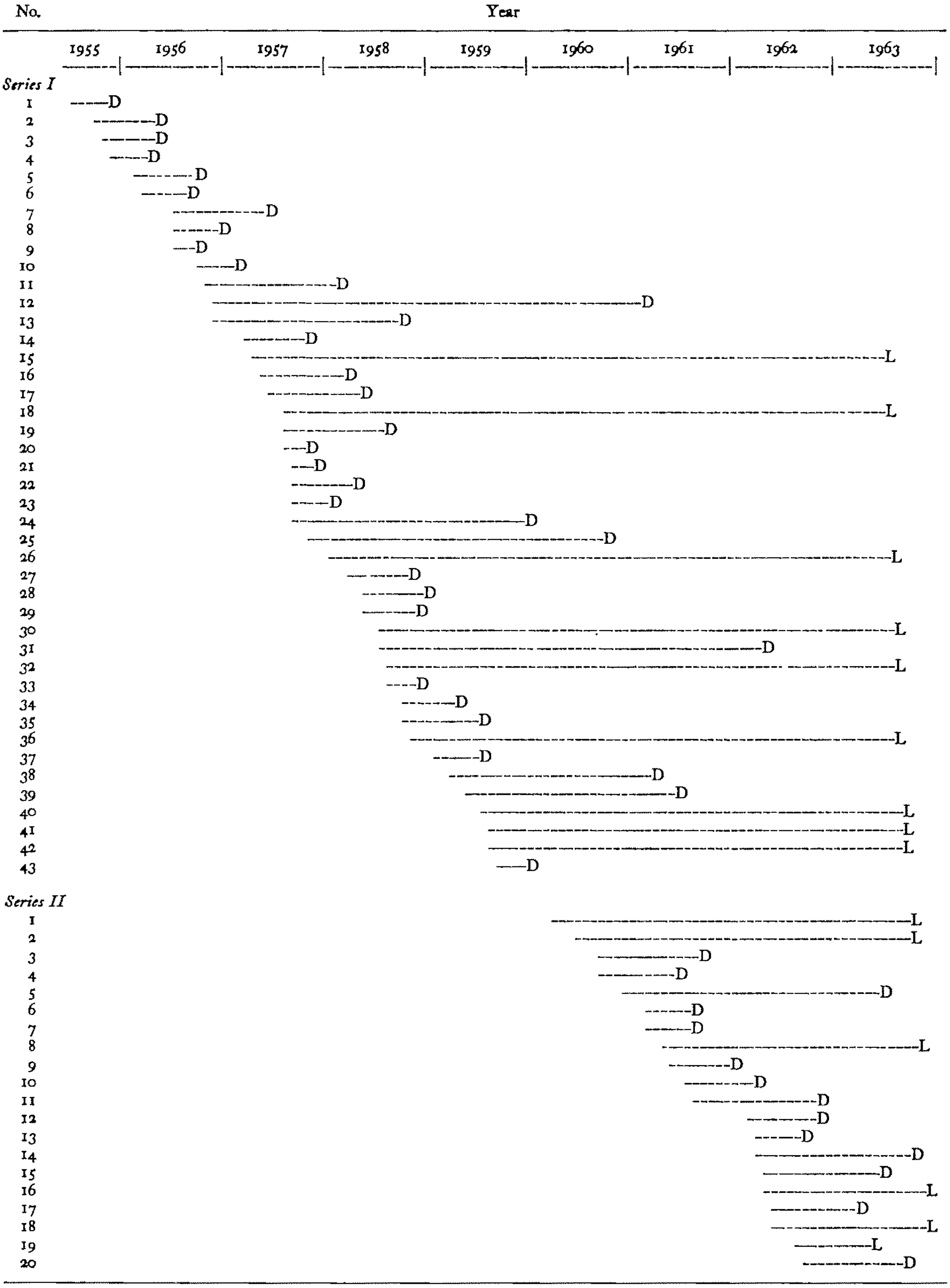
* The cell population turnover times of the human duodenum may be as short as 2 days (Bertalanffy, F. D., and Nagy, K. P. Mitotic activity and renewal rate of the epithelial cells of the human duodenum. *Acta anat.*, 1961, *45*, 362–370) and of the human colon and rectum as short as 4 days (Lipkin, M., Bell, B., and Sherlock, P. Cell proliferation kinetics in the gastro-intestinal tract of man. I. Cell renewal in colon and rectum. *J. Clin. Invest.*, 1963, *42*, 767–776). The cell population doubling times of human cancers of epithelial origin may be of many months' duration.[19,29,47]

TABLE IV

RESULTS IN SERIES I AND II CASES

Date of admission, length of life and status; L = living, D = dead



ably fractionated irradiation may be carried to high levels of dose, for the rate of restitution of the cancer cell population relative to its depletion rate by radiation injury will be very slow compared with that of those normal steady-state cell renewal, cell removal populations with very short cell population turnover times, and a cancericidal (cancer cell population depletion) effect may be attained without unacceptable injury to normal tissues. If, however, a high dose of radiation is given in a single sitting, then not only may the cancer cell population be destroyed but, also, the normal steady-state cell renewal, cell removal populations may be so depleted that restitution is impossible. Because of the great importance of this latter consideration, much attention is given in this report to the study and to the radiobiological interpretation of the radiation complications of the two Series of cases. If there is to emerge, for cancer not only of epithelial but of any other origin, an optimal relationship of dose and time appropriate to the radiotherapy of that cancer, then this relationship must be consonant not only with the destruction of cancer but with, also, the preservation in the normal tissues of their capacity for restitution.

RADIATION COMPLICATIONS

In cancer radiotherapy, while the effects of radiation on cancer may be beneficial to the patient, the effects of radiation on normal tissues are, in all respects, detrimental. It has already been suggested that these detrimental effects are not only the result of the radiation effects on cell populations but that they may also be due to unknown effects on the homeostatic regulators or the homeostatic regulatory mechanisms of the normal steady-state cell renewal, cell removal systems. Further, these detrimental effects may not be immediately manifest, for function may be preserved for extended periods in cells which have been lethally injured. At some period of cell reproductive or other activity, this latent injury will become manifest and restitution will be impaired. Such deleterious effects become manifest most quickly, but not necessarily most severely, in those tissues having the most rapid cell population turnover rates. The time variation of this sequence, injury—manifestation, may explain the early deleterious radiation effects observed in some tissues and the late effects observed in others without invoking differences in the inherent radiosensitivities of different tissues as the cause.

All of the complications which are listed in Table III were major ones; minor ones which may be acceptable under present day circumstances as unavoidable, such as slight or moderate degrees of mucositis, edema, dryness of the mouth, and pain are not included. It is apparent from the table that the incidence of radiation complications was substantially greater in the Series II than in the Series I cases and that this greater incidence was concentrated in the mucous membrane tissues of those functionally essential organs, the mouth, pharynx, and larynx. Of such complications, 13 appeared in the 43 cases of Series I and 38 in the 20 cases of Series II. Other complications were of about equal incidence in the two series.

The Series II cases were studied intensively in reference to salivary gland function[32] and nutritional states.[13] The salivary gland function studies showed elevation of the serum amylase from preradiation levels to 9 to 18 times those levels between 9 and 36 hours after irradiation of the total parotid gland mass. The nutritional states studies showed that by the application of appropriate feeding techniques (voluntary, nasogastric tube, pharyngostomy, or gastrostomy) and scrupulous dietary supervision both weight and nitrogen balance could be maintained in the postradiation period of severe reactions. If, however, circumstances precluded the application of appropriate feeding techniques, nutrition was not maintained in the presence of severe reactions and 1 patient died of a combination of cachexia and aspiration pneumonia.

The absence of major complications of skin and bone may be attributed to the so-called skin sparing effect in the case of the former and to the more favorable absorbed dose relationships, as compared with medium energy radiations, in the case of the latter and also, in the case of the latter, to the prior removal of teeth which would have been in the irradiated region. This clinical practice has been adopted empirically by many radiotherapy centers and the pathogenesis of osteoradionecrosis of the jaws is now sufficiently well understood to justify this practice on a rational basis. The key to the prevention of osteoradionecrosis seems, in the absence of such radiation doses as to be necrotizing regardless of mechanisms, to lie in the behavior of the normal steady-state cell renewal, cell removal system of the gingival epithelium. If the radiation dose level in respect to either single or fractionated applications is such that postradiation tissue restitution phenomena are not inhibited, then osteoradionecrosis will not supervene. This dose level may not be cancericidal. At higher dose levels, restitution phenomena will be delayed or inhibited, resulting in ulceration of the gingiva with extension of inflammation (infection) by way of the periodontal membrane through the lamina dura to involve the medullary cavity of the mandible and the apices of the teeth,[37] together with direct radiation effects on the osteocytes themselves and diminution of their capacity for repair.[30] It follows, then, that one component of the radiation injury which may result in osteoradionecrosis may be eliminated by prior extraction of teeth followed by a preradiation interval long enough to ensure closing and epithelization of defects so produced. It follows, likewise, that extraction of teeth following radiation injury of the mucosa and bone will open pathways of inflammation, as will the mechanical injury caused by ill-fitting dentures. The importance of the radiation dose level attained in the gingival mucous membrane and jaws and the role which a high dose level plays in the pathogenesis of osteoradionecrosis is exemplified by the high incidence of this lesion in a reported case series.[36] Of 251 cases of primary, untreated cancers of the anterior tongue, floor of the mouth, buccal mucous membrane, and lower gum, 93 developed osteoradionecrosis after radiotherapy and of these 74 had received either interstitial or a combination of interstitial and external beam irradiation.

Certain radiation fractionation experiments on the skin of swine[26] were interpreted as suggesting that the size and the number of radiation dose fractions, without respect to the interval between these fractions or the over-all time in which they are administered, are the determining factors of the degree of radiation injury and that, therefore, normal cell population restitution phenomena occurring simultaneously with the course of fractionated irradiation do not play an important role. The protraction time, 28 days, is, however, short in respect to the considerations developed in the preceding and it may be that even just a few more cell doublings occurring simultaneously with a longer irradiation course could be important in providing for the preservation of a postradiation cell regenerative base for restitution.* The difference may, in fact, lie between the preservation of a regenerative base and a nonregenerative effect. The frequency of radiation complications in the Series II cases as compared with those in Series I is interpreted as being, at extremes of fractionation-protraction effects, just exactly such a difference. For the effects observed, the pig skin experiments and their interpretation are valid; the question is to what degree they may be considered a model of cell population restitution and other effects. Studies of the dose and time relationship[8] suggest that values of n, in the dose-time equation, $D=kt^n$, are different for the cancericidal and skin tolerance effects (0.25 and 0.33, respectively). This difference is more probably the result of differences in the kinetics of repair and restitution between cancer cell and skin cell populations than of differences in radiosensitivities.

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* Professor Fowler very kindly reviewed a manuscript copy of this communication and has recently advised me that his interpretation of the swine experiments[26] is that cell population restitution phenomena were important in explaining the results: 5/6ths of the increase in dose with over-all time are interpreted as being due to recovery and 1/6th to cellular repopulation phenomena. This 1/6th represented about a hundredfold increase in the number of cells, an increase considered by Professor Fowler as highly important.

The occasional precipitate appearance of necrosis in irradiated tissue subject to mechanical trauma and the necessity, therefore, for invoking cell repair or repopulation phenomena indicate the incapability of the cellular potentiality for this response or the failure of homeostatic regulators or homeostatic regulatory systems or both. The cell population-homeostatic system may be capable of maintaining itself as a postradiation reduced steady-state system but it cannot respond to the added requirements for post-traumatic repair. Prolonged postradiation cell division delay with, finally, cell death in mitosis may explain the appearance of late, spontaneous necrosis as distinct from that which seems to be induced by physical trauma and there do, in fact, seem to be postradiation times at which the frequencies of the spontaneous necroses of different tissues are at highest incidence. Such considerations could explain the late appearance of necrosis in those steady-state cell renewal, cell removal systems with, presumably, very long cell population turnover times, such as connective and vascular tissues, cartilage, and bone and in those presumed steady-state, more or less fixed cell population tissues such as nervous tissue.

In terms of the quantum or biophysical phenomena of radiation injury, it has been emphasized that only the most general statements can be made about the mechanism of this injury.[41] It would be fatuous, therefore, to attempt an interpretation of the clinical observations in elaborate terms of biophysical phenomena, but this is not to say that it would not be profitable to undertake the correlative study of the two. It suffices, for the moment, simply to report the clinical observations and, at most, to speculate about the correlation of these with certain aspects of mammalian cell radiobiology and with what is known about the cell population kinetics of steady-state and non-steady-state systems. One cannot go too far here, either, for it is not presently known whether there exists a direct, inverse, or some other relationship between normal cell population turnover times and irradiation-depleted cell population replacement potentialities and postradiation turnover times. Some of the experimental aspects and theoretical implications of these considerations have been developed.[34,50] It would appear, if only on the basis of clinical observations of the postradiation state, that, invariably, the postradiation replacement potentialities or restitution processes are reduced and that cell population replacement times are increased.

None of the radiation complications of Series I and II cases can be attributed to the tissue defects resulting from the destruction of cancer, *per se*, as occurs, for example, in certain cancers of the esophagus where perforation may be attributed to the radiation destruction of cancer which has replaced the normal esophageal wall or to certain oral-cutaneous fistulas which may have a similar pathogenesis.

The clinical results attained in the Series I cases have been compared, in Table V, with other reported results of fractionated dose radiotherapy of similar cancers. The 3 year survival of the Series I patients is 30 per cent. Of the 17 groups listed in Table V, 15 report survival times greater than 1 year. Of these 15, eight are shown as having a 1 year or longer survival rate greater and 6 as less than the Series I three year, 30 per cent survival, cases. The consolidated 1 to 5 year survival of the 15 groups is 31 per cent while the 3 year survival of the Series I patients is 30 per cent. Within the limits of such comparisons, no differences can be shown between the survival rates for the more or less "conventionally" treated cases in Table V and the high dose, prolonged time radiation treated cases of Series I. Twenty-three autopsies were performed in the Series I cases; 20 of these examinations

TABLE V

RESULTS OF RADIOTHERAPY: REPORTS FROM OTHER SOURCES AND COMPARISON WITH SERIES I CASES

Reference No.	Site	Total	Survivals	Per Cent	Time (years)
36	Nasopharynx	84	33	39	5
	Tonsillar fossa	66	22	34	5
	Base of tongue	81	26	32	5
17	Mouth, paranasal sinuses, pharynx	119	16	13	3
33	Tonsils and pillars	105	30	28	1–4
	Vallecula	15	1	7	1–4
	Supraglottis	32	7	22	1–4
	Postcricoid	18	4	22	1–4
	Pyriform sinus	84	16	19	1–4
	Epiglottis	68	25	37	1–4
45	Palatine arch	259	56	22	3
51	Larynx, Stage III, extension beyond cords and fixation	78	33	42	5
18	Larynx, Stage II, anterior 2/3rd cord and commissure	12	7	58	1½–4
24	Tongue, anterior 2/3rd	68	29	43	5
	Floor of mouth, buccal mucosa, lower and upper gums	156	81	52	3
	Total	1,245	386	31	1–5
43	Mouth and pharynx	28	14*	50	1**
44	Mouth and pharynx	25	13*	52	1+**
Series I		43	13	30	3

* Control of primary lesion only.
** Mean observation time.

showed no residual cancer of the irradiated primary site of origin. If, however, complications were also reported in the cases in Table V, it may be that substantial differences in the incidences of such might be found which would relate to fractionation and protraction. It is probable, on the basis of all of the considerations developed above, that one pattern or interrelationship of dose and time is better, in terms of both cancericidal and normal tissue preservation effects, than another, but it is also probable that this better pattern will not be found by the haphazard adoption of the Series I, the 6,000 r over 6 weeks, the split dose, the split course, or any other named dose-time pattern but will only be found by systematic investigation.

Because of the sigmoidal shape of the mammalian cell x-ray or gamma-ray survival curve, increments of dose in the exponential region of it are relatively more effective than increments of dose in the shoulder region. Reference to Figure 2 shows, for the parameters of survival assumed for human cells, that single doses of

2,000 r would reduce the surviving fraction of a fully oxygenated cell population to the order of 10^{-6} and 2,500 r 10^{-7} and, conceivably, a cancericidal effect might result. This consideration was the basis for the treatment of the Series II cases. But such single doses also reduce surviving fractions of the cell populations of the normal tissues to the same level of probability and this level is sufficient to deplete them, as evidenced by the high incidence of complications in the Series II cases. There is, for comparison with the Series II cases, no published body of experience which is concerned with the cancericidal and normal tissues effects of large single external beam radiation doses administered to cancer of the upper food and air passages. Thirty cases of cancers of the head and neck have been reported[42] in which medium voltage x-ray exposures ranging from 2,000 r in a single sitting to 4,500 r in 4 days were administered and which, on account of the severity of the mucosal reactions, were standardized at 3,500 r in 5 days. Of the 30 cases so treated, only 3 were living at 3 years. It was concluded that epithelial cancers could be destroyed by the exposures administered but that an exposure of 3,500 r administered in 5 days was the maximum safe one insofar as the prevention of irreversible normal tissue damage was concerned.

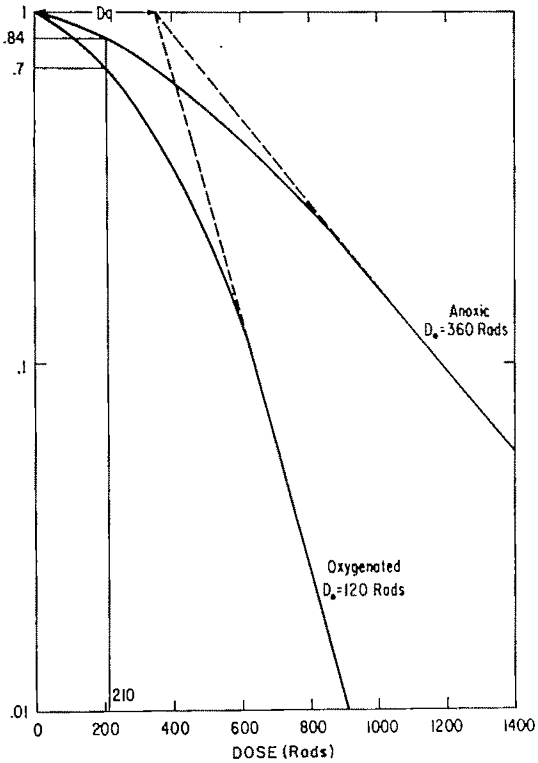

Fig. 3. Surviving fractions at small increments of dose in "shoulder" regions of survival curves.

Where two sigmoidal survival curves of different apparent radiosensitivities due to the oxygen effect are concerned, as shown in Figure 2, the ratios of doses required to attain given levels of surviving fractions will be least near the origins of these curves and will increase progressively as the curves diverge. These considerations suggest that the oxygen effect is least at very small doses. This concept is further developed in Table IV and Figure 3 where, for the given modal increment of fractionated exposure, 210 r, administered in the Series I cases, the surviving fraction of an anoxic cell population at this exposure is indicated, graphically, as 0.84 and of an oxygenated cell population as 0.7. If it may be assumed that these same surviving fractions of the viable cells remaining at the time of the first fractionated exposure are repeatedly attained with each fractionated exposure, then the cumulative surviving fractions for 43 increments of 210 r each will be, for the anoxic population, 0.84^{43} and the oxygenated population, 0.7^{43} or 5.5×10^{-4} and 2.2×10^{-7}, respectively. For single exposures of 2,500 r, as administered in some of the Series II cases, while the surviving fraction might be reduced to the region of 10^{-7} to 10^{-8} of an oxygenated population, it would be reduced to only about 2×10^{-3} of an anoxic population (Fig. 2). On the basis of these same parameters, if the critical cell population were a mixed one in respect to apparent radiosensitivity due to the oxygen effect and 1 per cent, only, of the cells were anoxic, then the cumulative surviving fraction under the fractionation technique of the Series

1 cases would be of the order of 5×10^{-5} and for the single irradiation, 2×10^{-5}.*

The many small fractions and the relatively long intervals between them (48 to 72 hours) permit certain restitution phenomena to occur simultaneously with the irradiation course; this is confirmed by the relative infrequency of major radiation complications and the oxygen effect is minimized at small increments of dose. An important corollary of this last is that if a few large dose fractions are to be employed then, because of the increase with increasing doses of the ratios of surviving fractions of cell populations having different apparent radiosensitivities, the oxygen effect must be minimized by some other means, presumably by irradiation in a high pressure oxygen environment. It is to be expected, then, that those performing clinical radiation studies under high pressure oxygen by the application of a few large increments of dose would demonstrate an oxygen effect without, however, the method necessarily representing the optimal technique.

DISCUSSION

The doses of radiation required for the control of human cancer of epithelial and epidermal origins are known in a general way as are also the effects of fractionation on these doses. This state does not obtain, however, in respect to a similar understanding of the radiation effects on the normal enveloping, supporting, sustaining, and lining tissues. It remains, then, to continue to investigate clinical practices so as to minimize these effects and to initiate such clinical and laboratory research studies as will contribute to the understanding and control of these normal tissue effects.

Highly competent criticism has been directed against the concept of the development of an optimal dose formula,[18,25] but the facts are that the limiting radiation reactions do not appear before but only following irradiation and they cannot, therefore, serve *per se* as useful guides to dosage in a given case and that in all radiotherapy clinics which publish their results a degree of standardization of practice by clinics exists. The degree to which a radiotherapy practice is standardized is a matter of some interpretation, and whether or not the practice is formalized as a set of rules or carried in the radiotherapist's head as a summed personal experience, it is still standardized. The effort to formalize radiotherapy practice on the basis of an increasing understanding of the biological parameters of the clinical radiation response will likely be rewarded in the same way that the understanding of the physical parameters of the radiation response has been. Further, some standardization at this time on an agreed upon basis will provide a better foundation for the intercomparison of radiotherapy practices and it will hasten the understanding of the biological parameters of the clinical radiation response. The efforts of the World Health Organization, of the International Union Against Cancer, and of the American Joint Committee[46] in the development of the staging of cancers and for the reporting of results have provided points of departure for the intercomparison of radiotherapy practices, for the systematic improvement of these practices, and for the orderly evolution of an optimal radiotherapy practice. This objective will not be so readily attainable if each radiotherapy center, uniquely, assumes a different position in respect to the biological parameters of the clinical radiation response as it might be if some standardization of or if some formalized intercomparison of these parameters, such as has been proposed by the Working Party of the British Institute of Radiology,[21,38] were undertaken.

CONCLUSIONS

In a general way, the optimal relationship of dose and time for both the cure of epithelial cancer and the least injury to the normal tissues is, for the greatest radiation effect in the former, that the radiation be administered in curative doses within the cancer cell population doubling time and, for the least radiation effect in the latter, that the radiation be fractionated in such a way that the interval between increments is longer than the cell population turnover time of the tissue for which this time is shortest and, to minimize the oxygen effect, that each increment of dose is in the shoulder region of the cell survival curve. The radiation should be administered within a cancer cell population doubling time for the avoidance of cancer cell re-population effects, increments of dose must not be at closer intervals than will allow normal cell repopulation effects to be manifest, and the final requirement is based upon the assumption that the oxygen effect is least for increments of dose in the shoulder regions of the survival curves. These conclusions and requirements suggest those presently unknown parameters of response of human cancer and normal cell populations which must be determined and suggest lines of research for their discovery. Cancer cell population doubling times can be determined by clinical and other studies; methods are available for the study of the kinetics of normal steady-state cell renewal, cell removal systems; and carefully designed dose fractionation studies will yield information on the magnitude of D_q and on the relative importance of the oxygen effect in the sigmoidal and exponential regions of the survival curves. Finally, although an optimal relationship of dose and time may be evolved by the clinical and laboratory studies of the variables suggested, such a relationship will remain theoretical until such a time as it can be tested on a formalized programmatic basis of cooperative group research. If, therefore, optimal patterns of dose and time relationships are to be found for a variety of clinical cancer situations, then definitive studies of these relationships must be undertaken systematically by the deliberate formulation of joint, cooperative, controlled large scale trials on a carefully elaborated clinical research protocol basis. Any such studies should include a small, widely spaced dose-increment and a greatly protracted irradiation group, after the Series I fashion, for the reasons that inhomogeneities of dose occurring at any given increment are more likely to be equalized at subsequent increments, that the oxygen effect is least important, that normal steady-state cell renewal, cell removal systems are least adversely affected, and that cancericidal effects can be attained. Quite the opposite considerations preclude any necessity for studies of single dose irradiations, after the Series II fashion.

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* The artificiality, noted in the previous footnote, of the use of the given parameters of response is readily apparent from the development of these numbers, for (oxygenated cell populations or not and over, presumably, some range of cancer cell population numbers) an important proportion of epithelial cancers is curable by radiotherapy. Cure implies, whatever the numbers developed, either the lethal injury by ionizing radiation of every cell of the cancer cell population or the interaction of other, presently unknown, factors.

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ADDENDUM

Reviewers of this communication have suggested that there be, for the sake of clarification, some further development of the concept that the oxygen effect ratio may be less at low than at high irradiation doses and of the implications of this concept. The determinant elements of this concept are the shapes of the survival curves, under both oxygenated and anoxic conditions, in their initial, low dose regions and these shapes have not, to my knowledge, been determined experimentally. A survival curve for oxygenated, only, mammalian cells has been experimentally determined quite accurately in this low dose region with an experimentally determined surviving fraction point at a minimum dose of 25 rads where the survival curve has an apparently limiting maximum value of D_0 of 450 rads. (BARENDSEN, G. W. Dose-survival curves of human cells in tissue culture irradiated with alpha-, beta, 20kV and 200kV X-radiation. *Nature,* 1962, *193,* 1153–1155.) The critical element in the effect being considered is, of course, the ratio of the value of the reciprocal of D_0 (oxygenated) to that of D_0 (anoxic) in the low dose region. It is very possible that in the low dose regions of the survival curves for mammalian cells the limiting maximum values of D_0 for both oxygenated and anoxic cell populations are approaching a ratio of unity. In such a case and if all else is equal, small fractions would be superior to large in respect to the oxygen effect in cancer radiotherapy.

Under conditions of fractionated irradiation where the time following the irradiation is both sufficiently long to permit recovery from sub-lethal radiation injury and sufficiently short that there will not be a significant increase in cell population by division of uninjured cells, then equal fractions will simply extend the survival curve along an exponential line drawn through the points of unity survival at zero dose and of the surviving fraction of cells after the first dose. It is probable that such conditions of irradiation as defined obtain in the tumor cell populations under consideration in this communication. When such exponential survival curves for fractionated irradiation under these conditions are constructed on the bases of the survival curves of Figures 2 and 4 of the text (which are not experimentally determined in their curvilinear regions but simply drawn) the following slope ratios of oxygenated to anoxic responses can be derived:

Dose increment (rads)	Slope ratio (oxygenated/anoxic)
210	2.1
600	2.4
1,200	2.9

A plot of these ratios shows, for the survival curves as drawn, a limiting value of 2. Theoretically, therefore, small increments of dose and fractionated irradiation would, under the irradiation conditions defined, be better in respect to the oxygen effect than large increments of dose. It is very desirable that an experimental model be evolved by which the theory may be tested.

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TREATMENT OF MALIGNANT TUMORS OF THE BREAST

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DURING the period from November, 1952 to July 31, 1960, 224 patients with malignant tumors of the breast were referred to the Department of Radiology of Sapporo Medical College. The patients were divided into two groups: (1) those who were referred for radiation therapy soon after operation either from our own surgical department or from other hospitals; and (2) those who were referred for treatment of recurrences or metastases several years after operation.

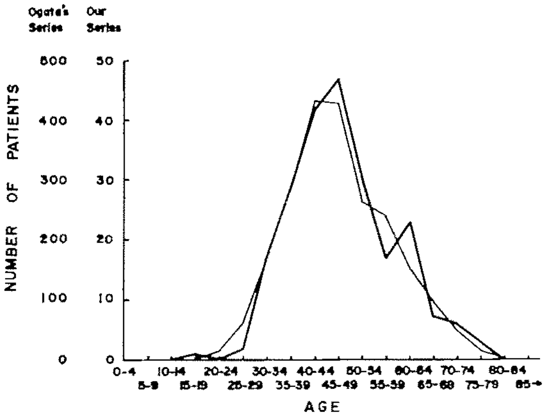

FIG. 1. Age distribution. The bold line represents the present series; the fine line Ogata and co-workers' nation-wide statistics based on 2,243 patients.

MATERIAL

As it is quite difficult to determine the exact time of onset of the disease, we assumed it to be, in the first group, the time when the patient was first seen in our department. In the second group, the onset was placed at the time of the first visit or operation at other hospitals. Figure 1 shows the age distribution of the patients in our series. The data are in good agreement with the nation-wide statistics of the age distribution reported in 1956 by the Research Group for Cancer Epidemiology by T. Ogata *et al.*[8] They show a rapid increase in the number of patients in the fourth decade with the highest rate of incidence in the fifth decade.

Out of 224 patients in our series 2 were males. Ogata and his co-workers found a male incidence of 2.05 per cent (46/2,243), and Isome and Tagaya[7] reported in their Tokyo University series an incidence of 0.45 per cent(4/896).

Malignant tumors of the breast seem to be somewhat more frequent in women with no children as compared to those with many children as shown in Table I.

In the reported cases, it appears that the left breast was slightly more often involved than the right breast. Smithers *et al.*[13] stated that an analysis of 13,152 cases of cancer of the breast showed involvement of the left side in 50 per cent, of the right side in 44 per cent, and, in 6 per cent of the cases, both sides were involved. In our series of 224 cases the left breast was involved in 136 patients, the right breast in 87, and both breasts in 1, the left breast being more frequently involved than the right breast with statistical significance ($P < 0.01$). Figure 2 shows the site of the lesions in 186 cases. The most frequently involved site was the upper outer quadrant of the breast.

The diagnosis of malignant tumor was confirmed histologically in 201 out of the 224 cases. As shown in Table II, the lesions were mostly adenocarcinoma and carcinoma simplex.

METHOD OF RADIATION THERAPY

Immediately following removal of the sutures, postoperative radiation therapy was started through five fields (Fig. 3). At first 160 kv., later 185 kv. was used, with 0.3 or 0.5 mm. Cu+0.5 mm. Al filter, 6 ma., and 30 cm. skin target distance, except on

TABLE I

NUMBER OF CHILDREN OF PATIENTS IN 224 CASES WITH MALIGNANT TUMORS OF THE BREAST

No. of Children	No. of Cases
0	53
1	29
2	30
3	31
4	19
5	22
6	16
7	9
8	8
9	2
10	2
Uncertain	3
Total	224

TABLE II

PATHOLOGIC DIAGNOSIS IN 201 CASES OF MALIGNANT TUMORS OF THE BREAST

Pathologic Diagnosis	No. of Cases
Papillary carcinoma	18
Comedocarcinoma	1
Adenocarcinoma	82
Carcinoma simplex	93
scirrhosum	
medullosum	
diffusum	
Squamous cell carcinoma	4
Carcinoma *in situ*	2
Sarcoma	1
Total	201

the anterior chest wall area where the skin target distance was 23 cm. A dose of 200 r in air per field was delivered daily to each of 2 fields, the fields being 10×10 cm. or 6×8 cm. in size. The axilla was irradiated through 2 opposed fields, the total dose being approximately 6,000 r in air. The supraclavicular area, anterior chest wall and sternal region were irradiated vertically, with total doses of 3,500 r in air to the supraclavicular area, and 3,000 r in air to the anterior chest wall and sternal region, respectively. If recurrences or metastases were noted after the first postoperative treatment, radiation therapy was given to these lesions as indicated.

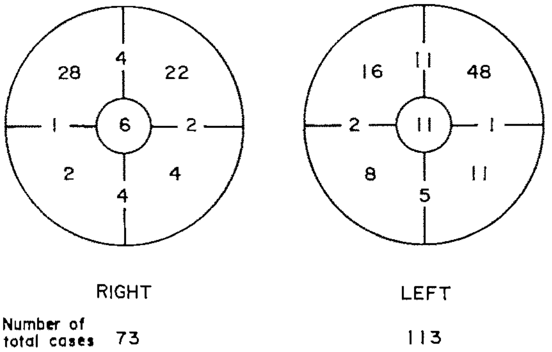

FIG. 2. Diagram showing localization of cancer of the breast. Figures indicate number of cases.

CLASSIFICATION

Various clinical classifications of the malignant tumors of the breast have been reported.[9,10,11,14] Excluding the recurrence group, we classified the new patients by the TNM system.[6] In our series, there were 41 Stage I, 61 Stage II, 61 Stage III and 1 Stage IV cases, or a 2:3:3 ratio. Nine cases were unclassified and 34 cases were in the recurrence group. There were three times as many Stage II and III patients as Stage I cases. It should be mentioned that only a few patients were diagnosed in the early stage, in spite of the fact that tumors of the mammary glands are easily palpable.

RESULTS

Follow-up studies were carried out on 207 patients out of 224. Seventeen patients were excluded: 11, because they were seen in consultation only and 6, since they were not examined histologically. Of the 207 cases, only 4 were untraced; 98.1 per cent

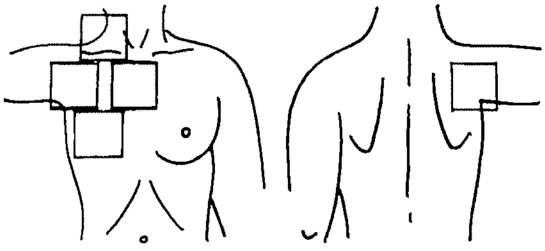

FIG. 3. Diagram showing the treatment portals.

Table III

OVER-ALL RESULTS IN 207 CASES OF MALIGNANT TUMORS OF THE BREAST

	Crude Survival Rate		Crude Survival Rate with No Evidence of Disease	
	No. of Cases	Per Cent	No. of Cases	Per Cent
1 yr.	174/207	84.1	108/207	52.2
2 yr.	132/187	70.6	96/187	51.3
3 yr.	84/144	58.3	66/144	45.8
4 yr.	59/117	50.4	51/117	43.6
5 yr.	43/93	46.2	38/93	40.9
6 yr.	30/73	41.1	29/73	39.7
7 yr.	18/47	38.3	18/47	38.3
8 yr.	7/22	31.8	7/22	31.8

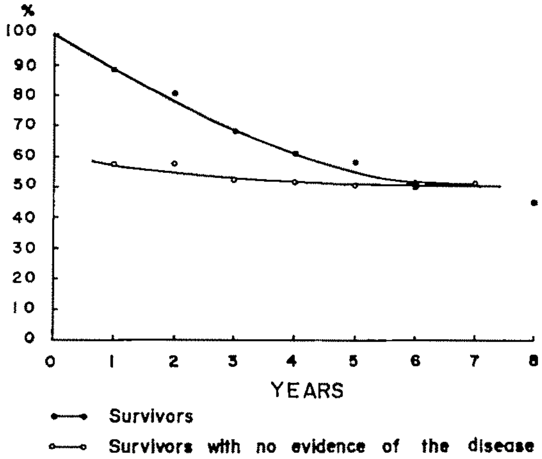

Fig. 4. Survival rate of patients with primary lesions corrected for expectation of life.

had complete follow-up. Out of 11 cases which were seen in consultation only, 3 were not treated as they were in a very poor condition, and the other 8 cases received treatment voluntarily elsewhere. The patients who could not be traced were assumed to have succumbed to carcinoma on the day they were last seen.

The over-all results in the 207 cases are given in Table III. The 3 and 5 year crude survival rates of these cases are 58.3 per cent and 46.2 per cent, respectively. Excluding the recurrence group of 34 cases, the crude 5 year survival rate is 54.4 per cent and the crude 5 year survival rate with no evidence of disease is 47.1 per cent as shown in Table IV. If these results are corrected, taking into account other causes of death by using a life-table, the 5 year survival rate is 58.8 per cent and the 5 year survival rate with no evidence of disease is 50.9 per cent (Table IV, Fig. 4). The crude 5 year survival rates are 75.0 per cent in Stage I, 56.5 per cent in Stage II, 47.6 per cent in Stage III and 24.0 per cent in the recurrence group (Table V). A comparison of 3 and 5 year results between cases diagnosed as adenocarcinoma and carcinoma

Table IV

RESULTS EXCLUDING THE RECURRENCE GROUP

	Crude Survival Rate		Crude Survival Rate with No Evidence of Disease		Survival Rate Corrected for Expectation of Life	Survival Rate with No Evidence of Disease Corrected for Expectation of Life
	No. of Cases	Per Cent	No. of Cases	Per Cent	Per Cent	Per Cent
1 yr.	152/173	87.9	98/173	56.6	88.9	57.2
2 yr.	122/155	78.7	87/155	56.1	80.6	57.5
3 yr.	75/114	65.8	57/114	50.0	68.5	52.1
4 yr.	52/90	57.8	49/90	48.9	61.5	52.0
5 yr.	37/68	54.4	32/68	47.1	58.8	50.9
6 yr.	25/52	48.1	24/52	46.2	52.9	50.8
7 yr.	14/31	45.1	14/31	45.1	51.1	51.1
8 yr.	5/13	38.5	5/13	38.5	44.9	44.9

TABLE V

RESULTS WITH RESPECT TO STAGES

		3 Year Survival		5 Year Survival	
		No. of Cases	Per Cent	No. of Cases	Per Cent
Stage I	Crude survival rate	21/27	77.8	12/16	75.0
	Crude survival rate with no evidence of disease	19/27	70.0	11/16	68.8
Stage II	Crude survival rate	29/38	76.3	13/23	56.5
	Crude survival rate with no evidence of disease	20/38	52.6	11/23	47.8
Stage III	Crude survival rate	21/40	52.5	10/21	47.6
	Crude survival rate with no evidence of disease	16/40	40.0	8/21	38.1
Stage IV	Crude survival rate	1/1			
	Crude survival rate with no evidence of disease				
Unclassified Group	Crude survival rate	3/8	37.5	2/8	25.0
	Crude survival rate with no evidence of disease	2/8	25.0	2/8	25.0
Recurrence Group	Crude survival rate	9/30	30.0	6/25	24.0
	Crude survival rate with no evidence of disease	9/30	30.0	6/25	24.0

simplex shows no significant differences (Table VI).

Of 173 cases having no recurrences or metastases when they were referred for radiation therapy, 68 or 39.3 per cent developed recurrences or metastases later.

TABLE VI

CORRELATION BETWEEN PATHOLOGIC DIAGNOSIS AND SURVIVAL

		Adenocarcinoma		Carcinoma Simplex	
		No. of Cases	Per Cent	No. of Cases	Per Cent
3 yr.	Crude survival rate	36/55	65.5	38/72	52.8
	Crude survival rate with no evidence of disease	29/55	52.7	27/72	37.5
5 yr.	Crude survival rate	19/37	51.4	17/33	51.5
	Crude survival rate with no evidence of disease	16/37	43.2	15/33	45.5

Table VII

CORRELATION BETWEEN NUMBER OF PATIENTS WHO DEVELOPED RECURRENCES OR METASTASES AND THEIR STAGES

	No. of Cases
Stage I	12/41
Stage II	22/61
Stage III	28/61
Stage IV	1/1
Unclassified Group	5/9

The clinical stages of these 68 cases are given in Table VII. Thirty-one were treated more than 5 years ago and they show a crude 5 year survival rate of 27 per cent (9 out of 31 cases) and a crude 5 year survival rate with no evidence of disease of 19.4 per cent (6 out of 31 cases). A comparison of these figures with those of the initially treated recurrence group reveals no significant difference.

The disease most frequently metastasized by lymphatic dissemination to the subcutaneous tissues of the operated side and to the adjacent anterior chest wall (Table VIII). Distant metastases were found most often in the bones, lungs, and liver. The lymphatic dissemination decreased as the postoperative period became longer, but the hematogenous dissemination was observed with the same frequency until 4 years after operation.

A comparison of the crude 5 year survival rate and the crude 5 year survival rate with no evidence of disease between 34 incompletely treated patients who missed radiation therapy through one or more portals for some reason, and 139 patients who completed the treatment through all 5 portals showed no statistically significant difference. Also, no significant difference was noted in the incidence of recurrences and metastases following irradiation between the 2 groups.

DISCUSSION

Evaluation of the cases comprising the series is of great help in analyzing the results of treatment. Benninghoff and Tsien,[1] in 1959, reported a correlation between the 5 year survival rate and the percentage of

Table VIII

RATE OF RECURRENCES AND METASTASES ACCORDING TO SITE AND YEAR AFTER OPERATION

	1st yr. (per cent)	2nd yr. (per cent)	3rd yr. (per cent)	4th yr. (per cent)	5th yr. (per cent)	6th yr. (per cent)	7th yr. (per cent)	Total (per cent)
Postoperative anterior chest wall	15.5	5.8	7.0	3.5	2.2	1.6		35.6
Axilla (operative side)	6.3	3.7	1.4	0.9	1.1	1.6		15.0
Axilla (opposite side)	1.4	0.5				1.6		3.5
Supraclavicular fossa (operative side)	6.3	3.7	0.7	4.4	1.1	1.6		17.8
Supraclavicular fossa (opposite side)	1.0	1.6		0.9		1.6		5.1
Skin of arm and back	0.5	1.1	3.5	0.9				6.0
Neck (operative side)	1.0		1.4	0.9		1.6		4.9
Neck (opposite side)	0.5							0.5
Opposite breast	0.5	0.5	3.5				2.6	7.1
Lung	5.3	3.2	4.2	4.4	1.1			18.2
Liver	3.9	3.2	3.5	1.8	1.1	1.6		15.1
Bone	3.9	3.7	5.6	6.1	1.1	5.0		25.4
Brain	1.9	2.1	0.7	2.6				7.3
Kidney	0.5	0.5	3.5					4.5
Pleura	1.4	1.6	1.4					4.4
Pericardium	0.5	1.1	1.4					3.0

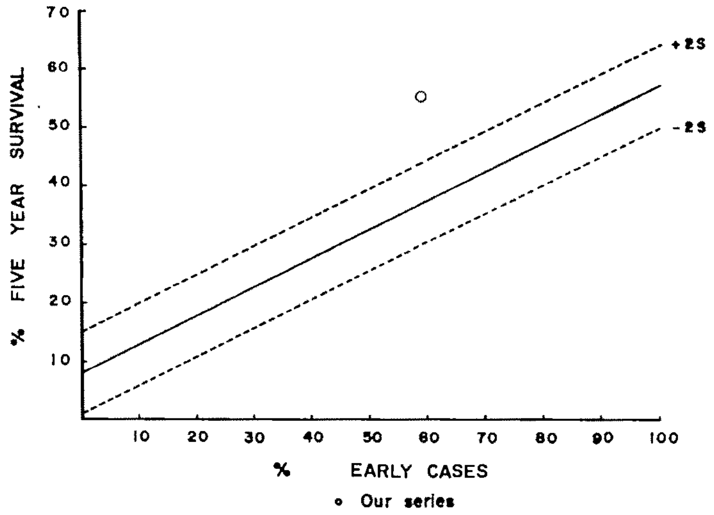

FIG. 5. Correlation between 5 year survival rate and percentage of early cases, showing our figure (o) against the plot of Benninghoff and Tsien.[1]

early cases, based on a summary of the results of treatment of previously untreated patients with cancer of the breast at various institutions. The center diagonal line in Figure 5 shows that the 5 year survival percentage at the various clinics was primarily influenced by the percentage of early cases, irrespective of the method of treatment. Benninghoff and Tsien's criteria for early cases were that the tumors be localized in the breast and axillary lymph nodes, and if palpable, that they be movable. Based on these criteria, it may be assumed that the Stage I and II cases of our series correspond to the early cases of Benninghoff and Tsien. Consequently, the percentage of early cases would be 57.4 per cent (39/68) and the 5 year survival rate of all our primary cases 54.5 per cent (37/68). The results of our series, if plotted, would appear above the upper dotted line of Benninghoff and Tsien's estimate (Fig. 5), thus indicating a somewhat better salvage rate.

A comparison of the 5 year survival rate (52.3 per cent) of our patients with metastases in the axilla (Stage II, III and IV) with those reported by other authors also shows a more favorable result (Table IX).

With regard to radiation therapy, no great difference between our present day methods and those employed at the Department of Radiology of Tokyo University around 1940 exists. Presently, the sternal region is also treated. In the earlier days 1 portal per day was irradiated, requiring more than 2 months for the treatment of the axilla, supraclavicular fossa and postoperative breast area, whereas at present 2 portals per day are treated, requiring a little over a month to complete the series and, when sternal port irradiation is added, a little over 45 days.

In view of the difficulty of determining the rate of recurrences or metastases even when there is a good general follow-up, in

TABLE IX

FIVE YEAR SURVIVAL RATES OF PATIENTS WITH AXILLARY METASTASIS AFTER RADICAL MASTECTOMY AND POSTOPERATIVE IRRADIATION

Authors	Period of Treatment	No. Treated	Per Cent of 5 Year Survivors
Endler[3]	1905–1944	336	41.7*
Diethelm[2]	1912–1945	619	43.2*
Smith and Smith[12]	1917–1946	210	41.4
Harrington[5]	1940–1944	692	39.6
Present series	1952–1956	44	52.3

* Values calculated from published data.

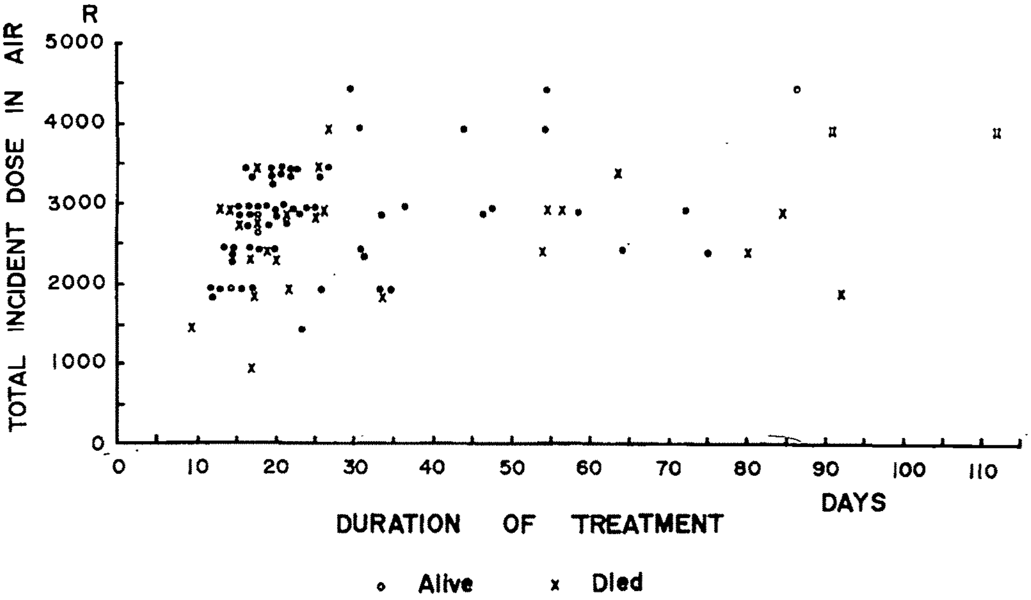

Fig. 6. The dose-time relationship in the treatment of the postoperative anterior chest wall in the early cases.

the present series the yearly number of patients developing recurrence and metastasis of a particular site after operation was divided by the number of patients followed in that year. In this manner the rate of incidence for each site and each year was calculated (Table VIII). While the reliability of this method may be questioned, since in cases observed over a long period a low rate will be obtained because of the decreasing number of cases, it enabled us to determine the incidence rate in cases of short observation with a certain degree of accuracy.

According to reports in the literature,[4,7] metastases in the skin of the anterior chest of the operated side are infrequent. In our series, the incidence at this site was high (35.6 per cent), exceeding that of the axilla and supraclavicular fossa.

Figures 6, 7 and 8 show the dose-time relationship of each irradiated field in early cases. No relation could be found between dose and survival, but the patients treated for a period longer than 50–55 days had a significantly more unfavorable prognosis. The rationale of such a long period of irradiation was based on the belief that rotation of the fields would allow the skin to recover and an increased total dose could be given. Accordingly, instead of completing irradiation of each portal, one by one, doses were delivered in a rotating manner. Starting with the anterior axillary field and supraclavicular fossa on the first day, the irradiation was shifted to the posterior axillary field and sternal region on the next day and the postoperative breast area was treated on the third day. The cycle was then resumed on the fourth day and so on. This method has now been discontinued since no indication of increase of skin tolerance was noted and there was no evidence of an effect on the survival rate.

SUMMARY

Two hundred and twenty-four cases of malignant tumors of the breast referred to our Department of Radiology from November, 1952 to July 31, 1960 were reviewed. Out of 224 cases, only 2 were males. Involvement of the left breast was significantly higher, being found in 136 cases. Histologic diagnosis was obtained in 201 cases, most of them showing adenocarcinoma and carcinoma simplex.

Out of 224 cases 17 were excluded. Of these, 3 were not treated because of the

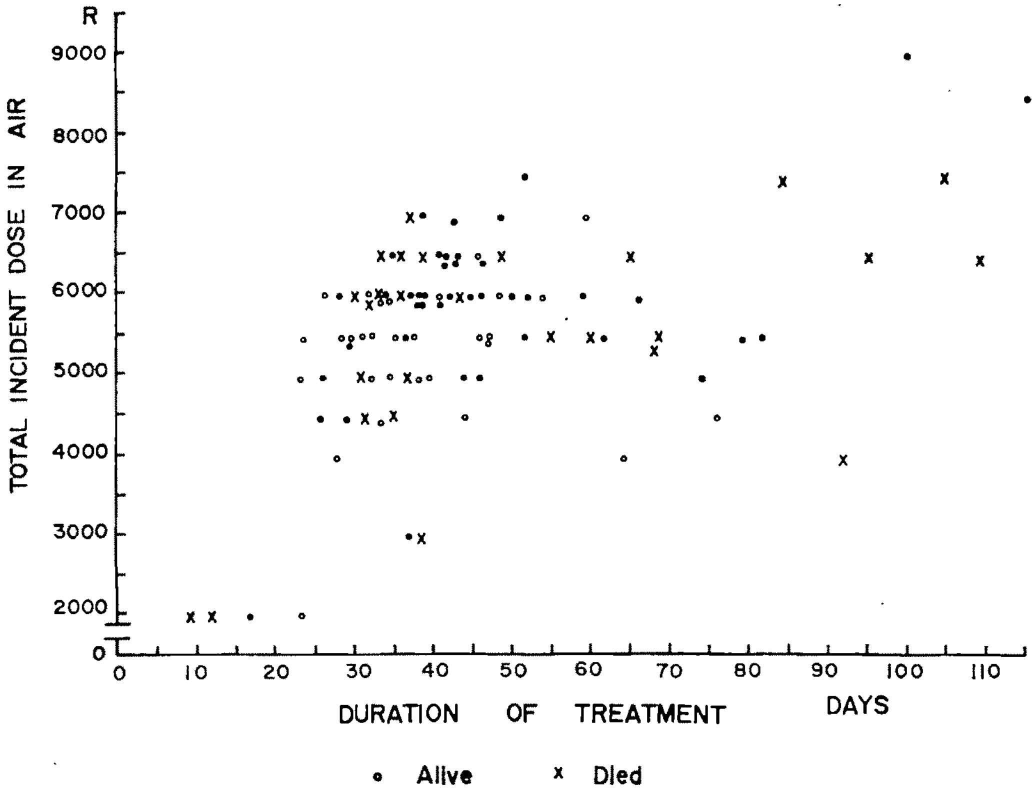

Fig. 7. The dose-time relationship in the treatment of the axilla in the early cases.

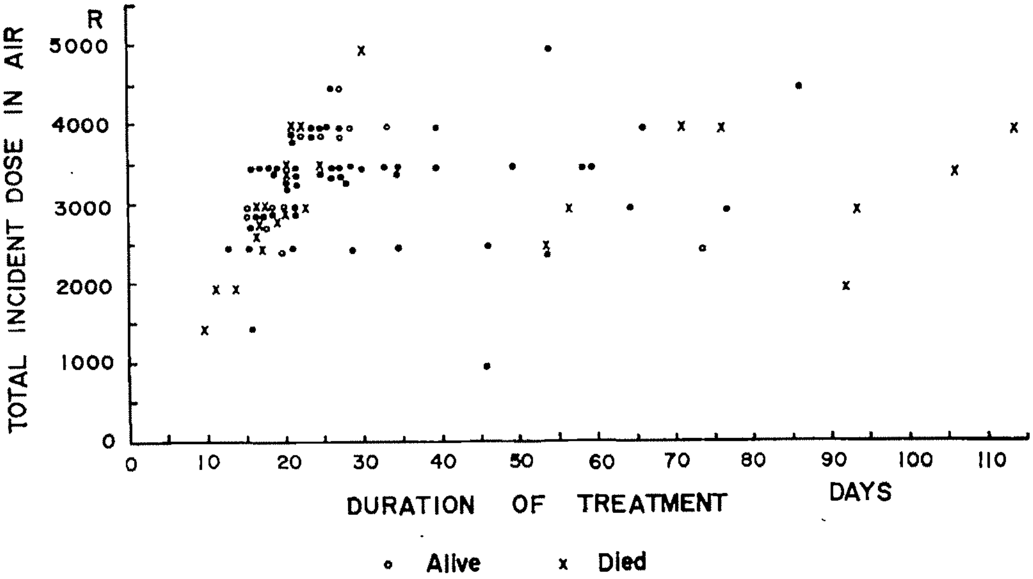

Fig. 8. The dose-time relationship in the treatment of the supraclavicular fossa in the early cases.

markedly poor general condition, 8 received treatment voluntarily elsewhere and 6 were not examined histologically. A follow-up study was carried out on the remaining 207 cases.

The patients were treated by mastectomy (mostly radical) and postoperative radiation therapy, using orthovoltage roentgen rays.

Patients with primary lesions who were referred for postoperative irradiation soon after operation were classified by the TNM system. Forty-one cases were placed in Stage I, 61 in Stage II, 61 in Stage III, and 1 in Stage IV; 9 were not classified. The percentage of cases being treated for the first time by irradiation for recurrence or metastasis was 16.4.

The crude 5 year survival rate of the cases with primary lesions was 75.0 per cent in Stage I, 56.5 per cent in Stage II and 47.6 per cent in Stage III. The crude 5 year survival rate of the entire series was 54.4 per cent and the crude 5 year survival rate with no evidence of disease was 47.1 per cent. Corrected for expectation of life, the crude 5 year survival rate was 58.8 per cent and the crude 5 year survival rate with no evidence of disease was 50.9 per cent. The crude 5 year survival rate of the entire series, including cases of recurrences and metastases was 46.2 per cent.

Metastases after treatment were noted most frequently in the skin of the operated area and the anterior chest wall.

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METHODS TO CONTROL CUTANEOUS AND SUBCUTANEOUS RECURRENCE OF BREAST CARCINOMA

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A MOST troublesome problem facing the radiotherapist is the recurrence of cancer within fields previously irradiated to the levels of skin tolerance. This often occurs in patients who have been treated for carcinoma of the breast. The development of cutaneous plaques or subcutaneous nodules is very distressing to most of these patients and additional treatment becomes imperative, not only to control the lesions but to spare patients the agony of witnessing growing cancer.

If roentgen therapy is the modality of treatment selected, it is necessary to use low doses and protract the course of therapy long enough to eradicate the lesions without producing ulceration. Since many of our patients come from distant stations, prolongation of treatment is not practicable. By taking advantage of the lack of backscatter and rapid fall-off of the intensity of the high energy photons of radium placed in molds or implants, we can complete our course of therapy in 3 days.

SYSTEM

We use the Paterson and Parker system.[1,2] This is a procedure that depends upon precise arrangements of low intensity radium sources. When this is accomplished, there is a uniform flux of photons at a chosen distance from the plane of the radium sources (Fig. 1). This distance is referred to as "h", and its value is selected to satisfy each pathologic situation. The resultant dose rate will be about 1,000 gamma r per day, and it is our experience that 3 days (3,000 gamma r) is sufficient to effect palliation.

The radium sources we employ are needles of 0.5, 1.6, 2, 3, and 4 cm. active length, 0.33–0.67 mg. per cm. linear density and 0.5 mm. platinum filtration. The needles are placed in molds to treat cutaneous lesions and buried interstitially to treat subcutaneous nodules. In each case we use a specific geometric pattern that satisfies the rules of the system, and any necessary or unintentional variation from it requires correction of the proposed time-dose relationship.

During their treatment patients are isolated in private rooms on a ward that employs trained and monitored radiation workers. When possible, these patients are paired to decrease loneliness. Safe distances for the other patients on the ward are determined by direct measurement with ionization chambers.

CUTANEOUS LESIONS

A suitable mold is fashioned from a 5 mm. thick slab of beeswax or paraffin to conform with the size and shape of the superficial cancer. Grooves that duplicate the required geometric pattern are carved into the face of the mold, and layers of elastic plaster are added to its undersurface until it becomes thickness "h". The mold is then loaded and the radium needles held in place by a cardboard cover.

The area to be treated is cleansed with alcohol and painted with benzoin; the mold is positioned and held fast by additional plastic tape. Roentgenograms are taken to confirm the location of the mold and record the pattern of the radium needles.

At the completion of the therapy the

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This material has been reviewed by the Office of The Surgeon General, Department of the Army, and there is no objection to its presentation and/or publication. This review does not imply any indorsement of the opinions advanced or any recommendation of such products as may be named.

mold is removed. The patient is informed that a brisk erythema will develop within the treatment area during the ensuing week, and that this will disappear with healing. She is also told to avoid prolonged exposure of the area to sunlight.

ILLUSTRATIVE CASE

An 86 year old Caucasian woman suffered from severe pruritus produced by two recurrent cutaneous lesions of mammary cancer. One of the lesions was 6 cm. in diameter and located on her back, the other was 2 cm. in diameter and located on her chest. Two years prior to this, each lesion had received 2,000 rads of orthovoltage roentgen irradiation in a single treatment. The lesions were retreated with radium molds that delivered 3,000 gamma r to each in 3 days. This caused cessation of the itching and marked reduction in size. Figure 2 shows the distribution of the radium sources in the molds.

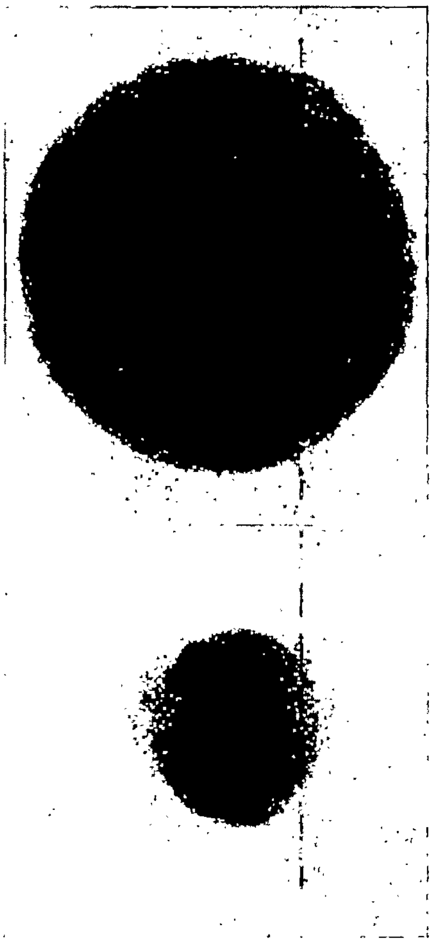

Fig. 1. Autoradiographs of the molds shown in Figure 2 demonstrating the uniformity of their photon flux at "h".

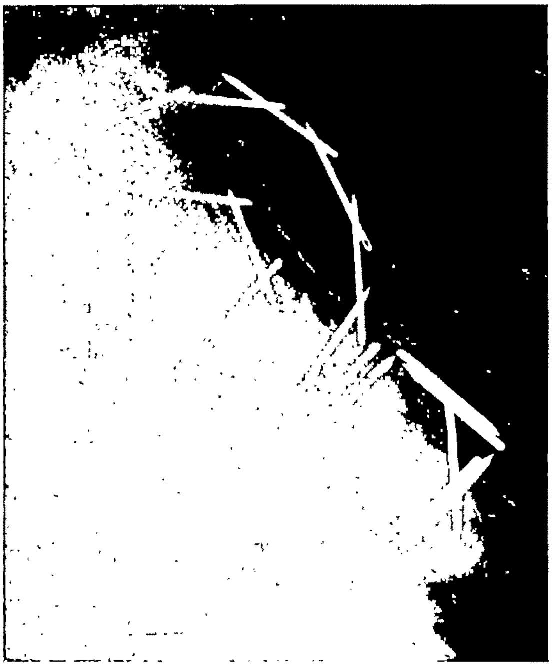

Fig. 2. Roentgenogram of two molds in place. The larger, duodecagonal mold is treating a 6 cm. diameter cutaneous lesion on the posterior chest wall and contains twelve 2 cm. and seven 1.6 cm. active length radium needles. The smaller, hexagonal mold is treating a 2 cm. in diameter cutaneous lesion on the anterior chest wall and contains ten 1.6 cm. active length radium needles.

SUBCUTANEOUS NODULES

Cancer which recurs under the skin in the form of nodules is ideal for implanting with radium needles. From the dimensions of the lesion a suitable pattern is determined; usually it is a single plane pattern.

We prefer the patient to have a light general anesthesia. The area to be implanted is cleansed with the standard skin preparations. Through small stab wounds the radium needles are inserted and buried at depth "h". Roentgenograms are taken to confirm the geometry of the pattern and, if no adjustments are necessary, the needles are sutured in place and the area is dressed.

At the completion of therapy the patient is given 100 mg. of demerol intramuscu-

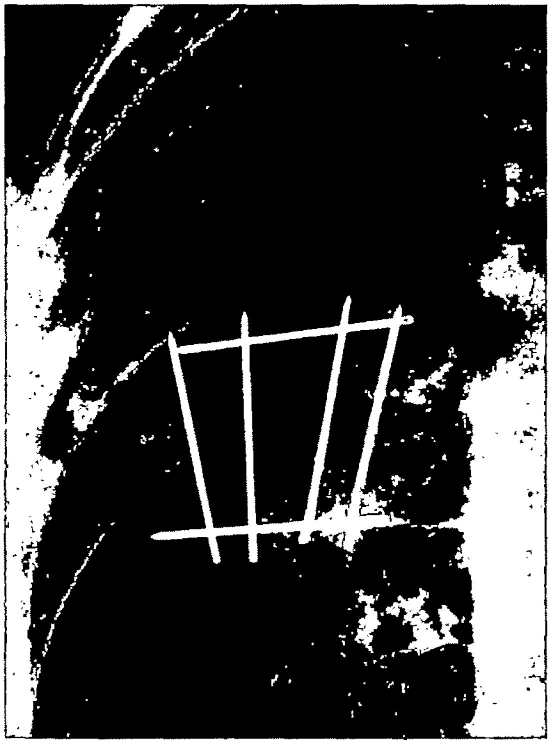

FIG. 3. Roentgenogram of a single plane implant treating a 3 cm. diameter subcutaneous nodule. It contains six 4 cm. active length radium needles. A 0.6 cm. active length radium needle is in a 0.5 cm. diameter nodule just medial to the area of the larger implant.

larly and the radium needles are removed. She is informed that a mild erythema will develop within the area during the next week and that it will disappear subsequently.

ILLUSTRATIVE CASE

A 46 year old Caucasian woman became acutely distressed when she discovered a 3 cm. diameter subcutaneous nodule in her anterior chest wall. Examination also revealed an 0.5 cm. nodule medially. She had received 3,500 rads to the chest wall a year earlier as part of her course of radiation therapy for carcinoma of the breast. The larger lesion was retreated with 6 radium needles in a single plane implant, and 1 needle was buried in the smaller nodule; 3,000 rads were delivered to each in 3 days. Her morale greatly improved as both lesions disappeared. Figure 3 shows the geometric distribution of the radium sources.

SUMMARY

Methods to control cutaneous and subcutaneous recurrence in patients who have cancer of the breast are discussed and examples of each are presented. The shortness of the period of treatment is stressed.

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ROENTGENOGRAPHIC SIGNS OF THROMBOSIS OF THE SUPERIOR VENA CAVA AND TRIBUTARIES IN NEOPLASTIC DISEASE*

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THROMBOSIS of the superior vena cava as a sole etiologic factor producing obstruction and the superior vena caval syndrome is a known, but infrequently encountered entity today.

Most commonly, malignant disease may cause superior vena caval syndrome due to compression or constriction of the superior vena cava, or due to invasion of the superior vena cava. Coexisting thrombosis secondary to compression or neoplastic invasion may preclude relief of the symptoms in superior vena caval obstruction by treatment directed toward the neoplasm alone, and worsens the prognosis. If recent thrombosis can be reasonably suspected roentgenographically by superior vena cavography, then rational treatment with thrombolytic agents concurrently with radiation or chemotherapy would be particularly indicated.

The present study deals with some of the roentgenographic signs which may be useful in attempting to differentiate between superior vena caval syndrome due to neoplasm alone and superior vena caval syndrome with associated thrombosis in the setting of neoplastic disease.

METHOD

Superior vena cavography was performed using the method of Robb and Steinberg. In general, bilateral cut-downs or percutaneously inserted Robb-Steinberg needles were employed using power injection with a twin syringe injector. Preliminary venous pressures were obtained as well as decholin arm-to-tongue circulation times on both sides. Where the arm-to-tongue circulation time was over 20 seconds, more dilute contrast material was employed. Otherwise, 30 cc. of 80 per cent angio-conray was used for each side. The injection pressure was relatively low (225 psi with a Taveras injector) and roentgenograms were obtained in anteroposterior and lateral projections for the most part. Immediately following each injection, a flushing dose of 50 cc. of saline with 5 mg. of heparin was administered through each needle. Roentgenograms were examined for location of occlusion, multiplicity of lesions, appearance of intraluminal filling defects and change on serial studies.

The 3 presently reported cases are selected in that all of the patients had clinically obvious superior vena caval syndrome. Figures 4 through 10 show other cases.

REPORT OF CASES

Case i. This 57 year old white male had been well until 2 months prior to admission at which time he developed cold, cough and chest pain which did not respond to the usual medications administered by his local physician. He was then admitted to another hospital and a lymph node biopsy of the supraclavicular area was performed and reported as adenocarcinoma. Following this, there was considerable progression of the patient's symptoms, mainly dyspnea, orthopnea, cyanosis and swelling of the head and neck until 4 to 5 days prior to admission to James Ewing Hospital.

Physical examination revealed a well-developed, well-nourished middle aged male in obvious distress with cyanosis and swelling of the head, neck and upper chest. Blood pressure was 90/60, pulse 120, respiration 124. There was diffuse fullness of the neck and bilateral supraclavicular masses, each approximately 4×5 cm. in diameter, with superficial venous distention

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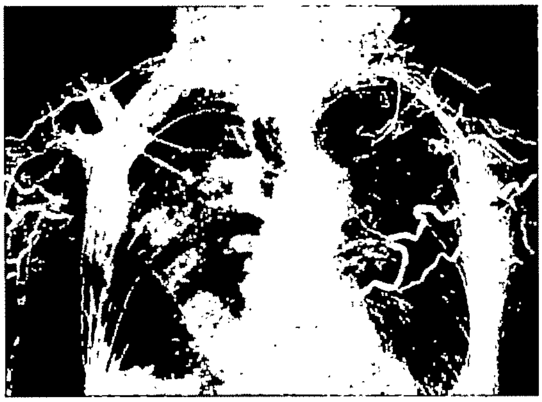

Fig. 1. Case i. *Superior Vena Caval Syndrome with Demonstration of Fresh Thrombus in Peripheral Vessels.* Complete nonopacification of the superior vena cava, both innominates and both subclavian veins, with collateral circulation primarily via the lateral thoracic and thoraco-epigastric routes. Note demonstration of intraluminal filling defects (arrows) in both basilic veins and left internal jugular vein. The findings were confirmed at autopsy.

in the neck and upper chest as well as in both upper extremities.

Chest roentgenograms showed a homogeneous density obliterating most of the right lung field with evidence of pleural changes and minimal blunting of the left costophrenic angle. A superior vena cavogram, made on an emergency basis, showed complete occlusion of the superior vena cava, innominate veins and subclavian veins, with definite demonstration of fresh thrombus in both basilic veins and in the left internal jugular vein (Fig. 1).

Treatment consisting of a combination of heparin and fibrinolysin commenced on November 8, 1963, the day after admission, and radiation therapy was started at the same time. In spite of the above combined treatment, there was a gradual downhill course, and the patient expired on November 12, 1963. The immediate cause of death was listed as respiratory failure.

At autopsy, the histologic diagnosis of terminal bronchiolar carcinoma of the right upper lobe with diffuse pulmonary lymphangitic carcinomatosis was confirmed, with metastases to the hilar and supraclavicular lymph nodes, vertebrae, diaphragm, and pericardium. There was direct invasion of the superior vena cava and thrombosis of the superior vena cava and the above described tributaries, the most peripheral of which showed fresh thrombi.

Case ii. This 54 year old white male was admitted to Memorial Hospital on July 6, 1960, with obvious superior vena caval syndrome secondary to carcinoma of the lung. He had had previous chemotherapy and radiation therapy in April, 1960, at another hospital. Two weeks prior to admission he developed varicosities over the anterior chest and cyanosis of his neck and arms.

A superior vena cavogram on July 30, 1960 (Fig. 2 *A*), showed filling of the right subclavian vein to its mid portion, located 5 cm. from the visualized margin of the tumor mass, and filling of the left subclavian vein only at its origin. There was some collateral circulation via intercostals and via the lateral thoracic and thoraco-epigastric pathways bilaterally.

He received a course of nitrogen mustard followed by orthovoltage roentgen therapy (2 mm. Cu half value layer) initially through a 12×19 cm. anterior midline field beginning on August 4, 1960. Later he was transferred to a 2 mev. Van de Graaff unit and received a final midline dose to the mediastinum through 12 ×19 cm. anterior and posterior fields of 3,710 r by August 31, 1960. Because of the initial impression on the cavogram that thrombosis was present, the patient was started on fibrinolysin therapy. Some clinical improvement was noted from the first week of August onward.

On August 16, 1960 (Fig. 2*B*), a second superior vena cavogram showed filling of the left subclavian vein which was attenuated by extrinsic compression at its junction with the left innominate, which was markedly compressed but showed some opacification on this study. There was now also opacification of the right subclavian up to its junction with the right innominate vein. At this time a large intraluminal filling defect having the typical characteristics of fresh intraluminal thrombus could be seen extending laterally as far as the vessel was visualized. In addition, there was now an intraluminal filling defect in the left axillary vein typical of a fresh thrombus.

Following completion of the patient's radiation and fibrinolysin therapy, there was a period of continued improvement. A third superior vena cavogram on September 7, 1960 (Fig. 2 *C*), showed further decompression of both innominate veins and the superior vena cava, all of which were still somewhat compressed, together with some visualization of the cardiac chambers for the first time, and evidence of partial lysis of

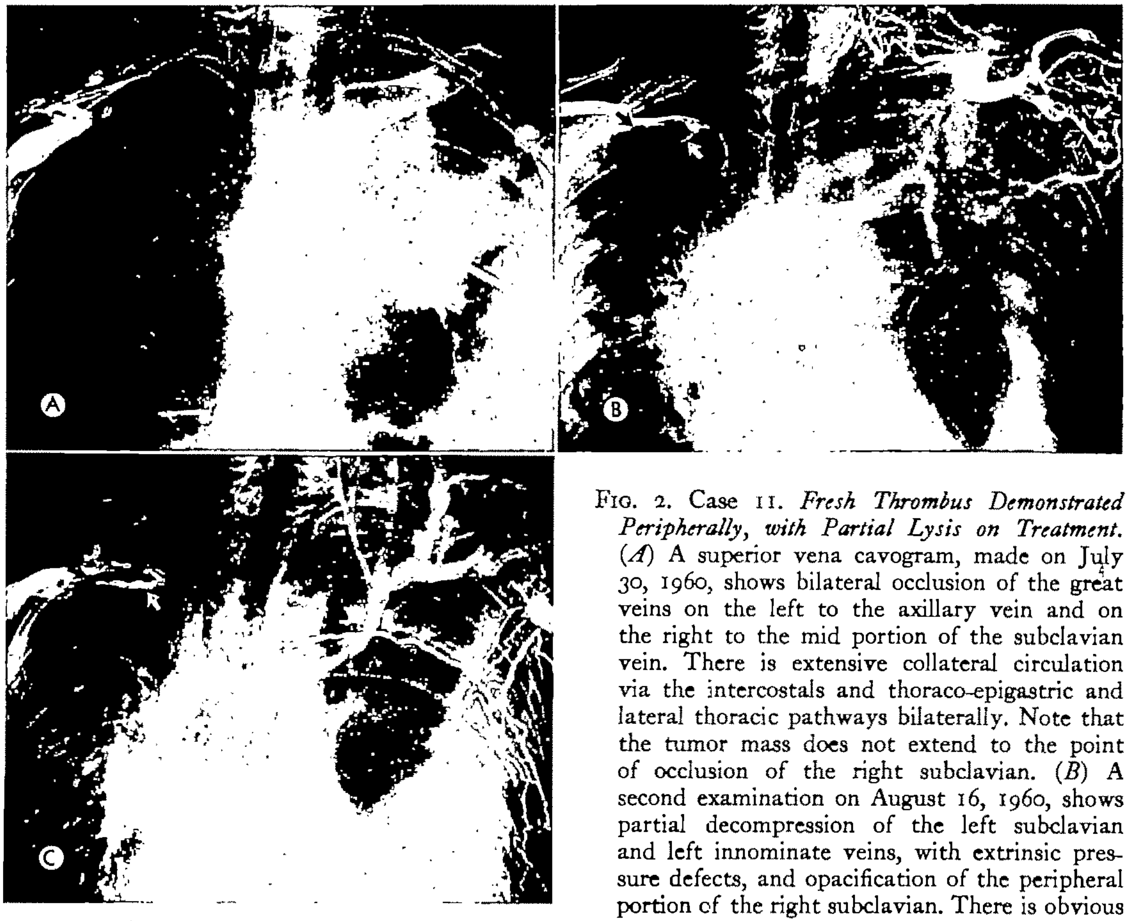

Fig. 2. Case ii. *Fresh Thrombus Demonstrated Peripherally, with Partial Lysis on Treatment.* (*A*) A superior vena cavogram, made on July 30, 1960, shows bilateral occlusion of the great veins on the left to the axillary vein and on the right to the mid portion of the subclavian vein. There is extensive collateral circulation via the intercostals and thoraco-epigastric and lateral thoracic pathways bilaterally. Note that the tumor mass does not extend to the point of occlusion of the right subclavian. (*B*) A second examination on August 16, 1960, shows partial decompression of the left subclavian and left innominate veins, with extrinsic pressure defects, and opacification of the peripheral portion of the right subclavian. There is obvious fresh thrombus (arrows) outlined by contrast material in the left axillary vein and in the visualized portion of the right subclavian vein. (*C*) On September 7, 1960, a third examination shows further decompression of the innominate veins and superior vena cava with partial lysis of the thrombus (arrow) in the right subclavian vein and nonopacification of the previously thrombosed portion of the left axillary vein, which is now probably completely thrombosed.

the thrombus in the right subclavian vein, even though this was outside the irradiated fields. The left axillary vein was now completely blocked.

Though the patient's superior vena caval obstruction appeared to have improved roentgenographically and clinically, by early October he became increasingly dyspneic and dysphagic, progressed rapidly downhill and expired on October 31, 1960.

At autopsy, there was only evidence of extrinsic compression of both innominate veins and the superior vena cava. The adjacent subclavian veins were explored and did not show any evidence of thrombus. The incision did not extend as far laterally as the axillary veins. The histologic diagnosis was anaplastic carcinoma of the lung.

Case iii. This 66 year old white female was first admitted to James Ewing Hospital on January 28, 1960, for a mass in the upper outer quadrant of the right breast. Biopsy revealed infiltrating duct carcinoma Grade ii, and radical mastectomy was performed. No involved lymph nodes were detected at any levels. The patient was discharged on February 2, 1960.

On July 3, 1962, the patient was seen complaining of exertional dyspnea. A chest roentgenogram showed a pleural reaction and an infiltrate in the right lower lung field. She was admitted to another hospital and was told that

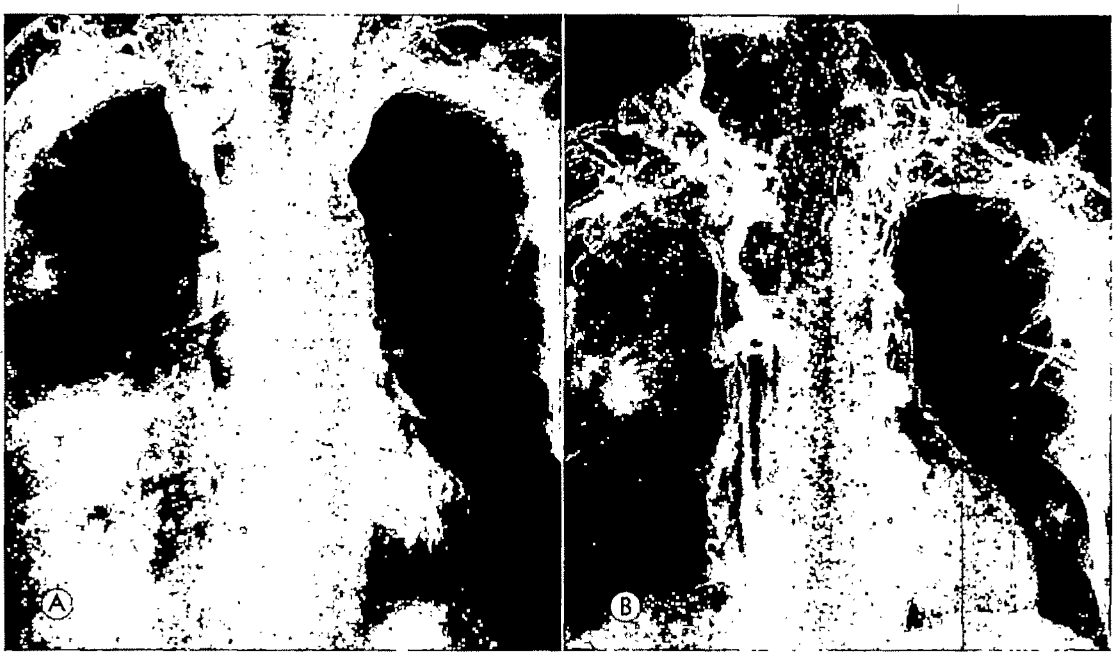

FIG. 3. Case III. *Probable Thrombosis following Radiation Therapy.* (*A*) Superior vena cavogram shows invasion of the right innominate vein and the superior vena cava by metastatic carcinoma of the breast, with partial obstruction. (*B*) Repeat examination following radiation therapy now shows complete obliteration of the innominates and the superior vena cava, narrowing of both subclavian veins, absence of filling of the left internal jugular vein, with an extensive collateral circulation via the azygos and hemiazygos, internal mammary, lateral thoracic, thoraco-epigastric and intercostal pathways. The rapid extension outside the area of visible tumor mass following radiation therapy suggests extensive thrombosis.

she had pneumonia, and discharged after 14 days. Her exertional dyspnea increased and she entered James Ewing Hospital on August 10, 1962. Widening of the middle mediastinum was noted on chest roentgenograms, and sputum cytology was reported as adenocarcinoma.

A superior vena cavogram at this time (Fig. 3 *A*) showed invasion of the right innominate vein and superior vena cava above and below the azygos vein resulting in partial obstruction. There was comparatively little collateral circulation.

The patient was treated through anterior and posterior fields to a tumor dose of 3,264 r on orthovoltage equipment. Following radiation therapy there was very little symptomatic relief.

A second superior vena cavogram (Fig. 3 *B*) now showed complete occlusion of both innominate veins and the entire superior vena cava, nonopacification of the left internal jugular vein, together with extensive collateral circulation via the superior intercostal and azygos vein on the right, the hemiazygos vein on the left, both internal mammary veins, and some contribution via the thoraco-epigastric and lateral thoracic pathways, as well as the intercostal pathways.

Diffuse osteolytic metastases were noted at this time and the patient was discharged to a nursing home for terminal care.

DISCUSSION

Until recent years, the majority of cases of superior vena caval obstruction were not associated with neoplastic disease. Brown,[5] in 1930, stated that 55 per cent of all obstructions were due to aortic aneurysm and only 25 per cent to carcinoma of the lung. Today, approximately 80 per cent of superior vena caval obstruction is found to be due to neoplasms.[10,20,23,27,28]

In 1936, Ochsner and Dixon[17] noted that 23 per cent of their cases of thrombosis of the superior vena cava were related to mediastinitis and 36 per cent to phlebitis, usually on an infectious basis such as syphilis or tuberculosis.

Failor *et al.*[10] have shown an incidence of thrombosis of 44 per cent in an autopsy series of superior vena caval syndrome due to carcinoma of the lung. More recently, Salsali and Clifton[22] show an incidence of 64 per cent under similar circumstances. This high incidence of thrombosis is apparently one of the causes for the poor prognosis in these patients, and especially the failure to respond to conventional treatment.[11,21]

Superior vena cavography in patients with obvious superior vena caval obstruction is useful in outlining the site and extent of disease; it influences the type of irradiation techniques; it can determine the need for retreatment,[13] and whether any current or new method of treatment is objectively successful; *i.e.*, whether the obstruction is relieved or whether symptomatic relief is merely due to the development of collateral circulation.

The demonstration of thrombosis is of prognostic significance[21] and valuable in management. Anticoagulant or fibrinolytic therapy is not always successful. Superior vena cavography should enable better selection of patients for this treatment,[18] especially if fresh thrombus which is not too extensive can be demonstrated.

With the upsurge of interest in vascular grafting, the exclusion of extensive thrombosis or occlusion by superior vena cavography in clinically obvious caval obstruction has acquired considerable significance.

The radiographic signs favoring the diagnosis of thrombosis of the superior vena cava and its peripheral branches in superior vena caval syndromes related to neoplastic disease are:

(1) *Peripheral venous occlusion at a distance from the radiographically visible tumor mass.* It is unlikely that retrograde venous invasion would occur at any great distance from the peripheral margin of the tumor mass.

(2) *Widespread multiple occlusions.* The presence of multiple occlusions in veins separated from each other by a considerable distance, such as occlusion of the right and left subclavian veins and the azygos vein would be unlikely with direct tumor invasion alone. However, a large tumor mass may completely occlude vessels over a fairly wide area without actual invasion or thrombosis. Demonstration of occlusion at a distance from the tumor mass would be a helpful corollary sign here.

(3) *Actual identification of an intraluminal thrombus.* When a thrombus is initially formed and represents a soft, retracted clot, it may not fill the entire lumen of the vessel and contrast material may surround it, resulting in demonstration of a fairly smooth intraluminal filling defect with contrast material between this defect and walls of the vessels. Since thrombosis occurs initially in the region of the neoplastic occlusion and with time proceeds in a retrograde fashion back along the tributaries of the superior vena cava, the most recently formed thrombus is always located most peripherally. This fresh thrombus is that which can be outlined by contrast material. Therefore, the demonstration of intraluminal filling defects at the periphery of the occluded vessels is of considerable importance in differentiating between thrombosis and tumor.

Several pitfalls in interpretation must be avoided, however. If the intraluminal filling defect is in the immediate area of the tumor mass it could well represent intraluminal tumor. Also, compression of a vein by a tumor mass causes flattening of the vein as it enters the tumor mass with resultant outlining of the lateral margins of the vessel by contrast material. Roentgenograms obtained in projections at right angles to each other demonstrating that the vessel is not merely flattened, but contains an intraluminal filling defect, would rule this possibility out. If the vessel can be seen in only one plane, it may taper at the point of compression suggesting extrinsic pressure.

If the intraluminal filling defect is not

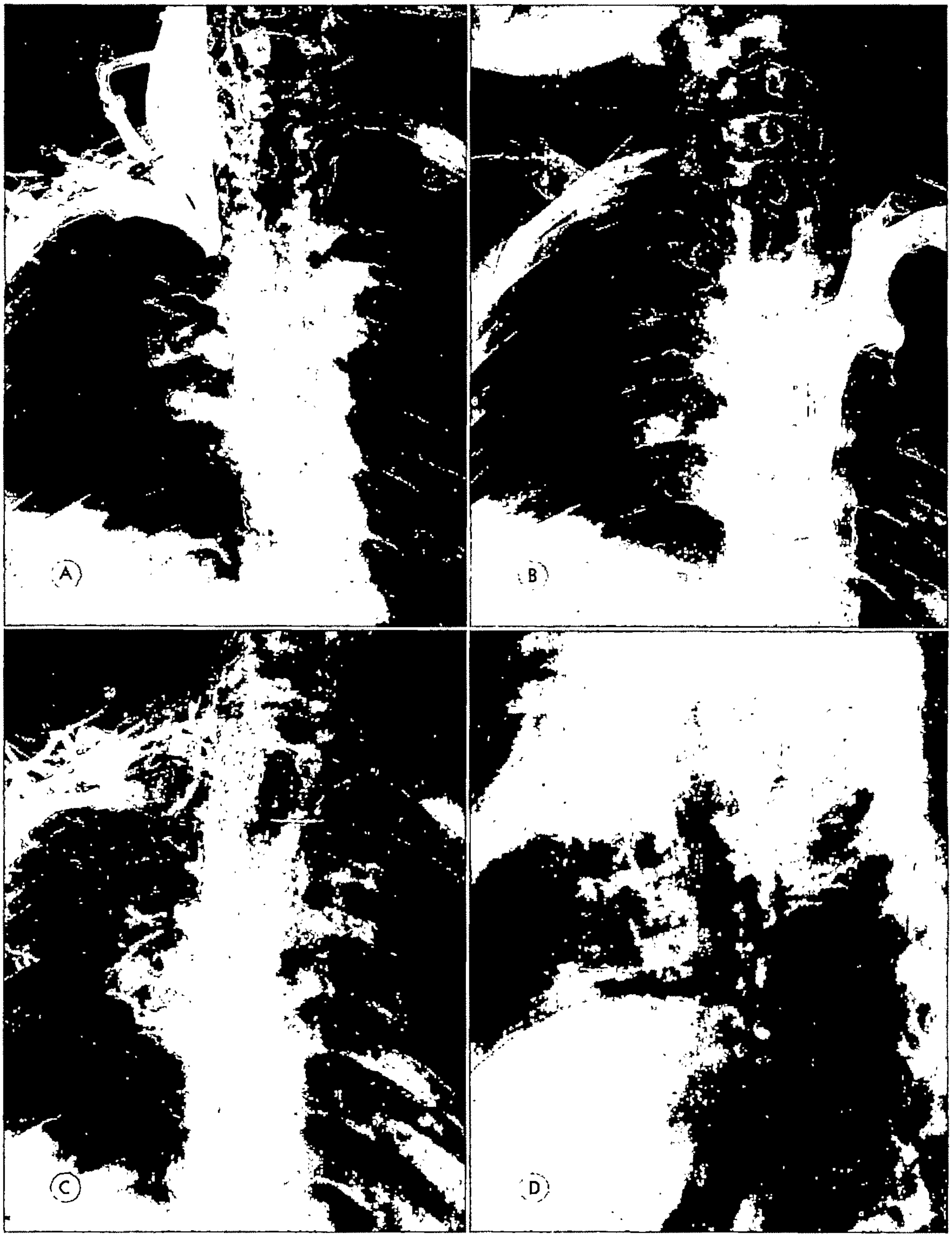

FIG. 4. Case IV. *Probable Thrombosis following Radiation therapy.* (*A* and *B*) A 37 year old Negro female with epidermoid carcinoma of the right lung, mediastinal invasion and superior vena caval syndrome. Right and left sided injections were performed separately and show tapering and occlusion of the right innominate vein and the left innominate vein, with collateral circulation via the accessory hemi-azygos vein on the left. (*C* and *D*) Following radiation therapy, the right sided injection shows nonfilling of the internal jugular

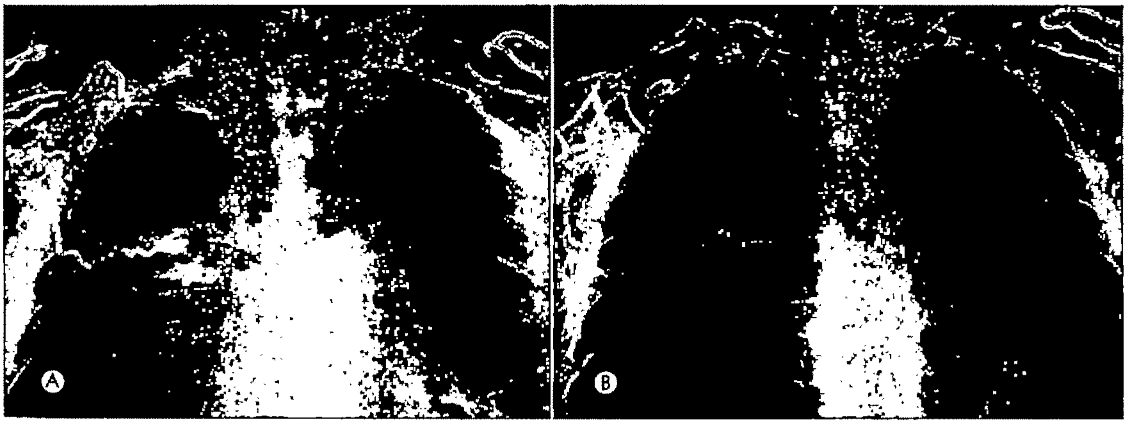

Fig. 5. Case v. *Peripheral Occlusion Unresponsive to Treatment.* (*A*) Superior vena cavogram of a 55 year old male following a 5,000 r tumor dose to the right upper lobe and mediastinum for epidermoid carcinoma proven by supraclavicular lymph node biopsy. There is nonfilling of the superior vena cava, both innominates and both subclavian veins, with some collateral circulation via the intercostals and thoraco-epigastric pathways. (*B*) Repeat superior vena cavogram 3 weeks later following treatment with nitrogen mustard, anticoagulants and fibrinolysin showed no improvement in the collateral circulation though there was some clinical improvement in the patient. The nonfilling of multiple main venous channels, including subclavian and axillary veins out to the periphery, well outside the known tumor area, is evidence of thrombosis.

located in the region of a tumor mass, one must be certain that it is persistent on several serial roentgenograms. As nonopacified blood washes contrast material out of a vessel after completion of the injection, if laminar flow is present, the fastest moving portion of the column will be in the center of the vessel so that contrast material may persist adjacent to the walls of the vessel on several roentgenograms even though it has been removed from the center of the vessel by the following column of nonopacified blood. Demonstration of a consistent filling defect on serial films is therefore important.

Occasionally, the degree of concentration of the contrast material may obscure the thrombus. Under these circumstances early roentgenograms in the series may outline an intraluminal filling defect and later roentgenograms obscure it. This is in contrast to the persistence of radiopaque material adjacent to the walls of the vessel on late roentgenograms after the central "core" of contrast material is washed away by a bolus of nonopacified blood.

(4) *Persistence or increase in the degree of occlusion on interval superior vena cavograms before and after treatment of the patient's neoplasm.* Since most neoplasms which cause

vein and proximal subclavian outside the area of visible tumor. The tumor mass itself is decreased slightly after 4,000 r to the mediastinum by cobalt 60 teletherapy. There is now collateral circulation via the superior intercostal vein to the azygos system. The extension of occlusion to an area outside the tumor mass with some reduction of the tumor mass following radiation therapy suggests that thrombosis has occurred.

superior vena caval syndrome are either anaplastic carcinomas or lymphomas, there should be some evidence of improvement in the patient's superior vena caval syndrome following radiation therapy if thrombus is not present. A decrease in the size of the tumor mass following radiation therapy with no improvement or worsening in the patient's occlusion noted on the superior vena cavogram may indicate that thrombus is present.

(5) *The presence of superior vena caval obstruction demonstrated by cavography following successful eradication of the patient's disease.*[7] Figure 7, *A* and *B* (Case VII) shows the appearance of a superior vena caval syndrome following successful eradication of the patient's carcinoma and possibly related to the patient's radiation therapy. The presence of a superior vena caval occlusion following successful treatment of the patient's disease and apparent eradication after a suitable period of time would favor thrombosis.

Signs favoring occlusion on the basis of tumor are as follows: (1) compression or extrinsic pressure; (2) no decrease in the size of the tumor mass following radiation therapy; and (3) a short polypoid, irregular intraluminal filling defect in the region of the patient's visible tumor mass.

SUMMARY AND CONCLUSIONS

1. There is a high incidence of thrombosis associated with superior vena caval syndrome due to neoplasm.

2. In many cases extensive thrombosis

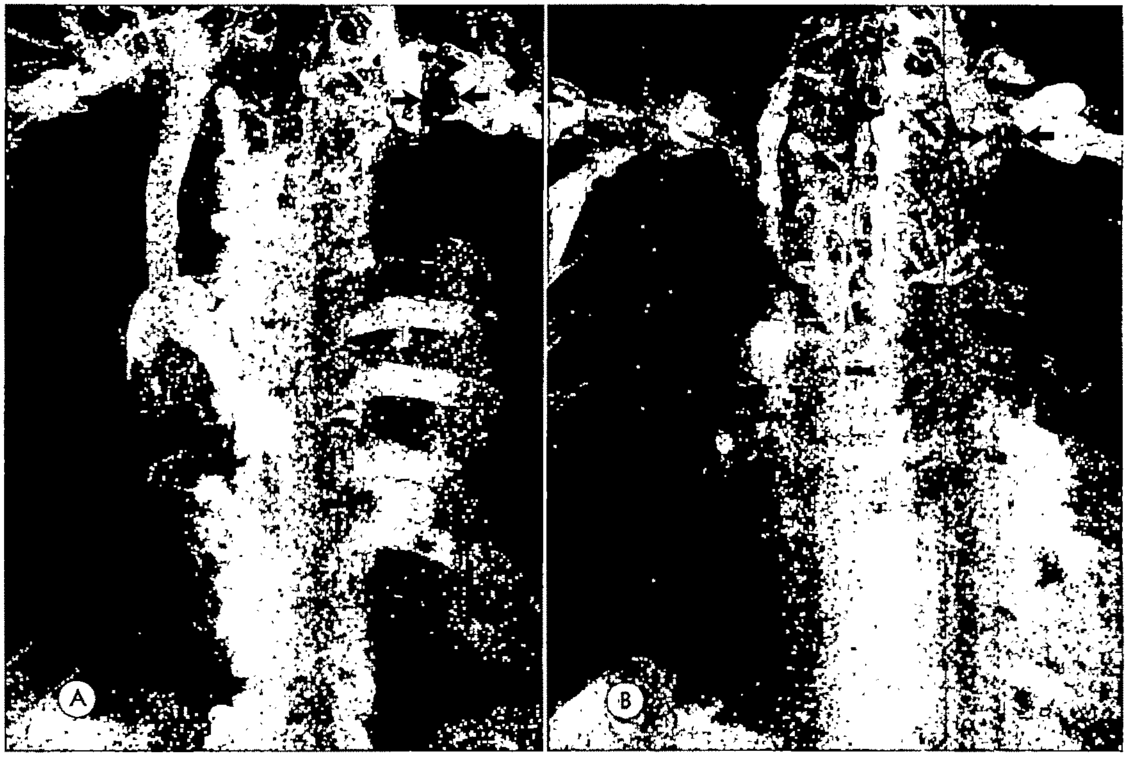

Fig. 6. Case VI. *Peripheral Filling Defect Persisting after Radiation Therapy.* (*A*) Superior vena cavogram prior to treatment in this patient with malignant lymphoma shows a lesion in the left subclavian vein just proximal to the junction with the internal jugular vein, approximately 3 cm. outside the patient's visible tumor mass. There is also blockage of the lower superior vena cava with collateral filling of the azygos system and the vertebral veins. (*B*) Following radiation therapy to the occluded areas there is a decrease in the size of the mediastinal tumor mass and opening of the superior vena cava but persistence of the filling defect in the left subclavian vein which probably represents thrombus.

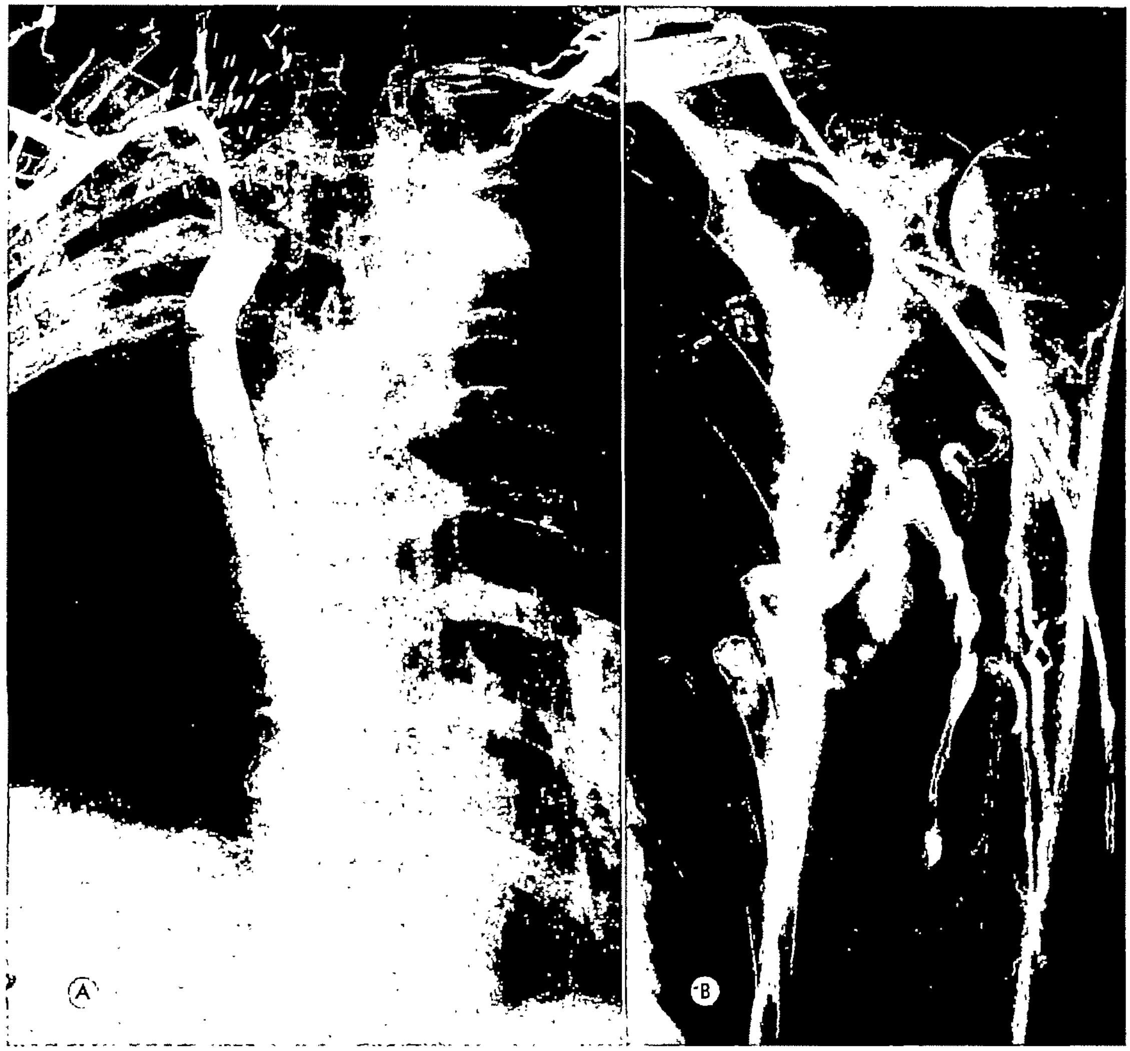

Fig. 7. Case vii. *Thrombosis 10 Years following Treatment of Carcinoma of the Lung.* (*A*) This patient had a proven epidermoid carcinoma of the lung which was treated with partial resection and a radon seed implantation as well as external orthovoltage roentgen therapy 14 years previously. Four years ago he developed superior vena caval syndrome. This has been fairly stable ever since. There is narrowing of the right subclavian, innominate and external jugular veins in the region of the radioactive implant and complete blockage of the left innominate vein. (*B*) There is blockage of the left axillary vein and collateral circulation via the thoraco-epigastric and lateral thoracic pathways. The 10 year time interval between the treatment of the patient's bronchogenic carcinoma and the appearance of the superior vena caval syndrome, together with the lack of progression of the superior vena caval syndrome and other changes during the past 4 years, indicate that the above findings probably represent widely separated areas of thrombosis.

can be demonstrated on superior vena cavograms.

3. Signs favoring the diagnosis of thrombosis include: (a) peripheral venous occlusion at a distance from the radiographically visible tumor mass; (b) widespread multiple occlusions; (c) visualization of fresh intraluminal thrombus; (d) failure to decompress the obstruction after radiation therapy, particularly if shrinkage of the tumor mass is seen; and (e) persistence or development of superior vena caval obstruction long after successful treatment of the patient's neoplasm.

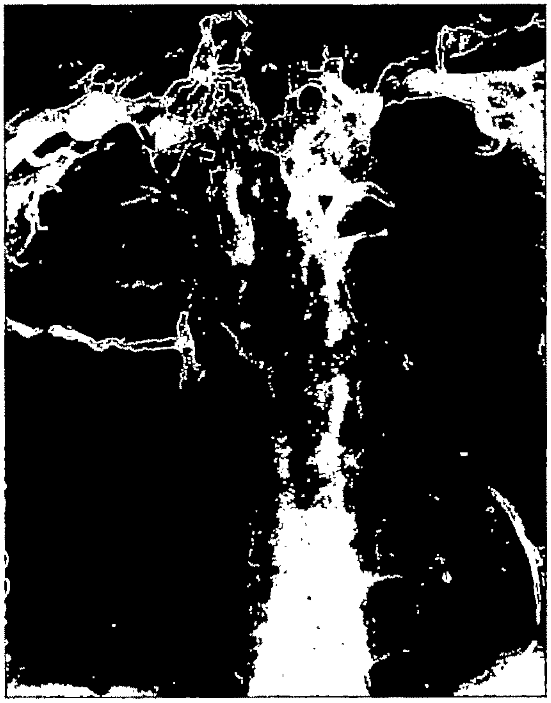

FIG. 8. CASE VIII. *Multiple Venous Occlusions at the Periphery of the Tumor Mass.* This patient had an anaplastic carcinoma which failed to respond to 4,115 r by cobalt 60 teletherapy. A superior vena cavogram made several months after treatment shows occlusion of the innominate veins at the periphery of the tumor and filling of the azygos system via the superior intercostal up to approximately the level of the tumor mass. Though there appears to be an intraluminal filling defect in the proximal right innominate vein, the tapering of the vein at this point at the margin of the tumor suggests that this could represent a compression phenomenon rather than a true intraluminal filling defect (arrows). None of the areas of occlusion visualized in this patient are significantly outside the confines of the tumor mass. Therefore, it is uncertain whether thrombosis exists.

4. Demonstration of thrombosis by superior vena cavography may contribute to the patient's prognosis and management.

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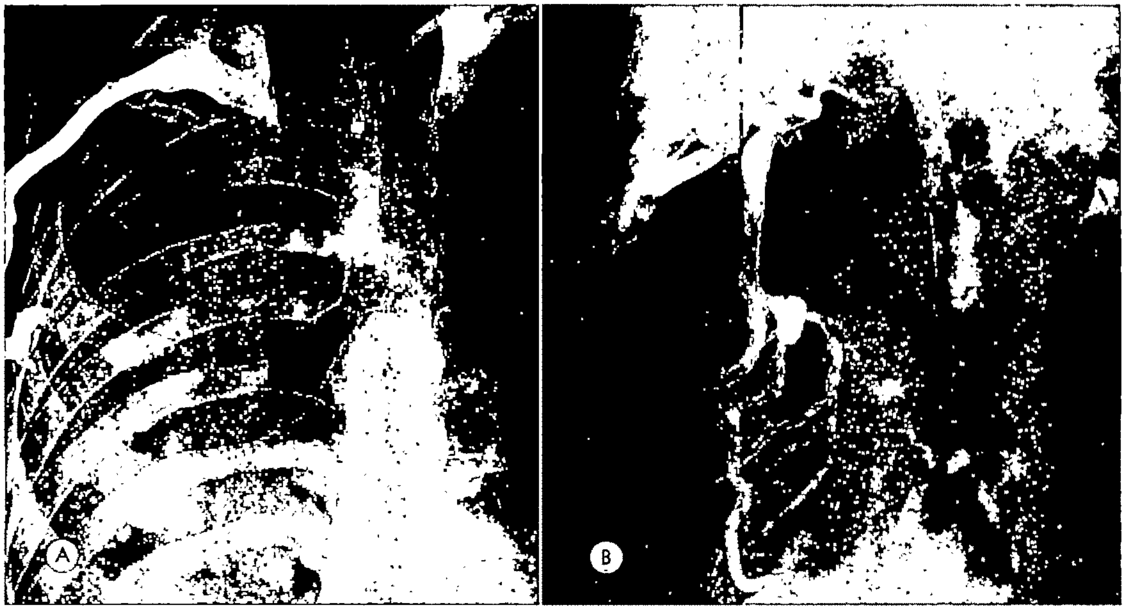

Fig. 9. Case ix. *Superior Vena Caval Syndrome without Evidence of Thrombosis.* (*A*) This 48 year old white male with Hodgkin's disease and superior vena caval syndrome was thought to have a possible intraluminal filling defect at the junction of the right subclavian and internal jugular veins. At autopsy, no thrombus was found, but the huge tumor mass did compress this area causing tapering and flattening of the vessel. (*B*) Note that the right innominate vein cannot be visualized on the lateral roentgenogram due to other overlying opacified vessels. Without biplane projections, caution must be exercised in interpreting suspected filling defects near a tumor mass, especially if tapering is present.

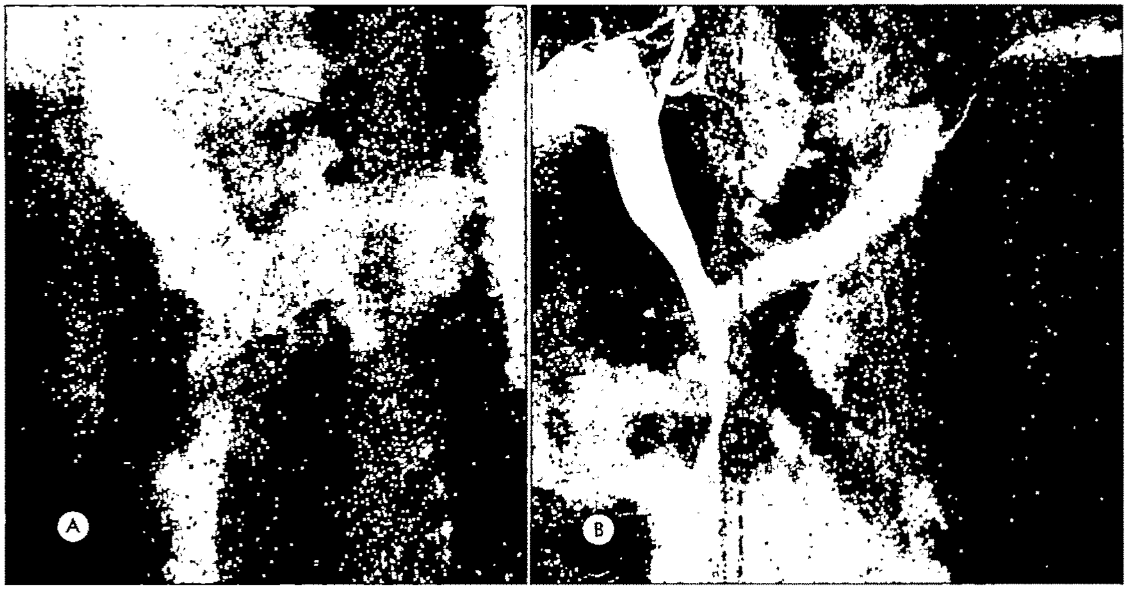

Fig. 10. Case x. *Tumor Invasion of Superior Vena Cava.* (*A* and *B*) Typical ragged polypoid intraluminal filling defect at the level of the azygos in the region of the patient's tumor characteristic of invasion of the vessel by tumor.

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RESULTS OF RADIATION THERAPY IN PATIENTS WITH INOPERABLE CARCINOMA OF THE LUNG WHOSE STATUS WAS ESTABLISHED AT EXPLORATORY THORACOTOMY*

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THE study reported here from the Francis Delafield Hospital of the Columbia Presbyterian Medical Center in New York City does not include patients with operable carcinoma of the lung, or questionable cases. Only patients with inoperable carcinoma of the lung were accepted for external irradiation, with the intent to find out what results could be achieved with definitive radiation therapy under proper approach and management. In the beginning, all patients with inoperable lung lesions were treated with ionizing radiation, whether they were found to be inoperable on clinical grounds, or at the time of an exploratory thoracotomy. The evaluation of this first group has shown that symptomatic relief was achieved in 75 per cent and that a number of patients showed an increase in their life span.

Encouraged by these findings, the next phase of this investigation was directed to patients who had had an exploratory thoracotomy, but were found to have an unresectable lesion at the time of surgery. This group represented more favorable patient material, inasmuch as there was no clinical evidence of inoperability and no proof of distant metastases. This project seemed to be of special importance, since many surgeons and radiologists do not advise radiation therapy after an unsuccessful thoracotomy as long as the patients are asymptomatic. Our study shows, however, that radiation therapy can be of definite value in such instances.

Table I

MICROSCOPIC CLASSIFICATION OF 95 PATIENTS WITH UNRESECTABLE CARCINOMA OF THE LUNG AT THORACOTOMY

Squamous cell carcinoma	52	68
Anaplastic carcinoma	12	
Oat cell carcinoma	4	
Carcinoma		14
Alveolar carcinoma		1
Adenocarcinoma		10
Thymoma		1
Mesothelioma		1
Total		95

One hundred and forty patients, who had undergone an exploratory thoracotomy but in whom the lesions were found to be unresectable, were treated between July, 1955 and July, 1963. This report deals with the 95 patients who had received a full course of supervoltage therapy before March, 1961, thus allowing at least a 3 year follow-up. In all of these cases, the diagnosis was verified by microscopic examination of the tumor. Patients who were not referred for radiation therapy immediately after the exploratory thoracotomy, but some months later for symptomatic relief or for the treatment of metastases, are not included.

The microscopic classification of the 95 patients is shown in Table I.

The treatment approach has been a rather uniform one. A total tumor dose of 5,000 rads was delivered in a period of 5 weeks through large opposing fields, includ-

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TABLE II

PERTINENT DATA ON 8 PATIENTS WITH UNRESECTABLE CARCINOMA OF THE LUNG AT THORACOTOMY LIVING 3–9 YEARS AFTER RADIATION THERAPY

	Pathologic Diagnosis	Reasons for Inoperability	Survival Time
MF	Squamous cell carcinoma	Extension and mediastinal involvement	9 years
HB	Squamous cell carcinoma	Extension and mediastinal involvement	9 years
AH	Thymoma	Invasion of right auricle and superior vena cava	8 years, 5 months
SM	Squamous cell carcinoma	Extension and mediastinal involvement	7 years, 7 months
VR	Carcinoma	Extension and mediastinal involvement	6 years
EK	Squamous cell carcinoma	Extension and mediastinal involvement	4 years, 2 months
SC	Squamous cell carcinoma	Extension and mediastinal involvement	3 years, 3 months
AK	Squamous cell carcinoma	Invasion of right hilus and pulmonary artery	3 years

ing the mediastinum, on a 2 million volt roentgen ray unit, with a half value layer of 7 mm. of lead and a target skin distance of 100 cm. Neither rotation therapy, nor scanning, had been used, as it is believed that the preservation of the unimpaired function of the healthy opposing lung is essential for survival.

An analysis was made of patients who had lived over 3 years after therapy in order to see whether the type of tumor, or the findings at the time of surgery, had any influence on the outcome. Seventeen patients were in this group and 8 of these patients are still alive.

In Table II pertinent information is given on the 8 patients who are still alive for periods from 3 to 9 years. Six of these cases were unresectable because of extensive mediastinal involvement, 1 showed invasion of the auricle and superior vena cava, and 1 of the right hilus and pulmonary ar-

TABLE III

PERTINENT DATA ON 9 PATIENTS WITH UNRESECTABLE CARCINOMA OF THE LUNG AT THORACOTOMY LIVING AT LEAST 3 YEARS, BUT DYING LATER

	Pathologic Diagnosis	Reasons for Inoperability	Survival Time
SG	Squamous cell carcinoma	Diffuse lymph node involvement including the mediastinum	5 years
BS	Mesothelioma	Diffuse invasion of pleura	4 years, 3 months
AS	Adenocarcinoma	Extension and mediastinal involvement	4 years, 2 months
LS	Carcinoma	Extension and mediastinal involvement	4 years (suicide)
PM	Carcinoma	Pleural invasion	3 years, 10 months (lost for follow-up)
CD	Carcinoma	Solid fixation of tumor to apex of left rib cage and invasion of parietal pleura; tumor encompassed 1st rib, 1st interspace, 2nd rib and 2nd interspace	3 years, 10 months
JK	Oat cell carcinoma	Extension and mediastinal involvement	3 years, 8 months
BR	Squamous cell carcinoma	Widespread disease in lower lobe, pericardium, aorta, pulmonary vein and parietal pleura	3 years, 8 months
WJ	Squamous cell carcinoma	Tumor extension into lateral pleura and peribronchial lymph nodes	3 years, 3 months (autopsy—widespread disease)

tery. Six of these patients had squamous cell carcinoma, 1 tumor was diagnosed as carcinoma only, and 1 was a thymoma.

In Table III data are presented on 9 patients who had lived at least 3 years, but who have since died. There were 3 squamous cell carcinomas, 1 oat cell carcinoma, 3 carcinomas, 1 adenocarcinoma and 1 mesothelioma. Five of the patients in this group had, in addition to other evidence of widespread disease, pleural involvement, which is known to be of grave prognostic significance, and which may have had a bearing on the outcome. Only 1 of these patients died in the hospital; the autopsy showed widespread disease. One of the patients, who appeared to be free of disease at the time of his last clinic visit, 2 weeks before death, committed suicide because of unhappy family circumstances. No autopsy was performed.

As shown in Table IV, of the total group of 95 patients in the series, 55 have been alive for 1 year or more; 26 patients have lived longer than 2 years; 17 patients have lived more than 3 years; 11 patients have lived more than 4 years; and 7 patients have lived 5 years or longer, some of these patients are still alive.

In Table V, the survival rates of this patient material, where the inoperability became evident only after thoracotomy, are compared with those of the previously reported group of patients who were considered to be inoperable clinically. As was to be expected, a striking improvement in the survival time of these patients, when compared with the first group, was noted. This is evidenced by the following survival rates: 1 year, 57.9 per cent versus 40 per cent; 2 years, 27.3 per cent versus 13 per cent; 3 years, 17.8 per cent versus 7 per cent; and 4 years, 11.5 per cent versus 5 per cent. The 5 year survival rate of this group of patients is 7.4 per cent—a figure which may increase when we will have a complete 5 year follow-up of this patient group. The average survival time is 21 months, as compared to 10 weeks-6 months in the untreated patients.

Table IV

SURVIVAL RATES IN 95 PATIENTS WITH UNRESECTABLE CARCINOMA OF THE LUNG AT THORACOTOMY

Total No. of Patients	95
Alive more than 1 year	55
Alive more than 2 years	26
Alive more than 3 years	17
Alive more than 4 years	11
Alive more than 5 years	7

Table V

COMPARISON OF THE SURVIVAL RATE OF 95 PATIENTS WITH UNRESECTABLE CARCINOMA OF THE LUNG AT THORACOTOMY AND 150 PREVIOUSLY TREATED PATIENTS, WHO WERE EITHER CLINICALLY INOPERABLE OR UNRESECTABLE

	Clinically Inoperable		Inoperable Disease at Thoracotomy	
No. of Patients	150		95	
Survival Time	No. of Patients	Per Cent	No. of Patients	Per Cent
12 months+	58	40	55	57.9
24 months+	19	13	26	27.3
36 months+	10	7	17	17.8
48 months+	7	5	11	11.5
60 months+	4	2.5	7	7.4

These figures take on an even greater significance when the data recently published by Pack and Ariel concerning resectability and survival rates in 4,814 patients with pulmonary carcinoma, which were collected from 6 large clinics in the United States, are considered (Table VI). Although not specifically mentioned in this report, it may be assumed that the patients who survived 5 years were those in whom resection of the tumor was possible. This would leave

Table VI

RESECTABILITY AND SURVIVAL RATES IN PULMONARY CARCINOMA DATA COLLECTED FROM 6 CLINICS IN THE UNITED STATES

Total no. of patients	4,814
Explored	2,792
Resected	1,637
5 year survival	412
5 year survival of explored patients	14.75%

Table VII

EVALUATION OF 20 PATIENTS AFTER INCOMPLETE SURGICAL PROCEDURE

Total No. of Patients	20	Reasons for Postoperative Radiation Therapy	
No. of patients after lobectomy	14	Tumor left behind in	
No. of patients after pneumonectomy	6	Mediastinum	8
Microscopic Classification		Veins and pericardium	2
Squamous cell carcinoma	8	Tumor found in parietal pleura	6
Undifferentiated squamous cell carcinoma	7	Tumor cut through with close margin	4
Adenocarcinoma	5		

1,155 patients of the explored group who did not survive 5 years, compared with a 7.4 per cent survival of our unresectable patient material. Although our figures are still small, they are significant when we take into consideration, not only the 5 year survival, but also the patients who benefited from radiation therapy for 1, 2, 3 and 4 years.

There is in our material a third group of 20 patients who should be mentioned, as their evaluation has yielded some interesting data. These are patients who were referred to our department for radiation therapy after a lobectomy or pneumonectomy had been performed in other hospitals and where disease had been left behind. In the evaluation of these patients the same criteria were used as in the patients with unresectable carcinoma of the lung. Only such patients who were referred for radiation therapy immediately after surgery, and who had received a full course of therapy were studied. Patients who were referred for radiation therapy more than 2 months after surgery, or patients who did not complete the course of therapy, were not included in this group. In Table VII information on the surgical procedure which had been carried out, on the extent of the disease at the time of surgery and on the microscopic diagnosis in these 20 patients is presented.

Table VIII

SURVIVAL RATES IN 15 PATIENTS AFTER INCOMPLETE SURGICAL PROCEDURE AND POSTOPERATIVE RADIATION THERAPY

Total No. of Patients	20
Died in 3–9 months	15
Died in 9–13 months	5

Note: The average survival time in these patients was 7½ months.

Autopsy findings in 4 patients were generalized and local disease in 2 and generalized but no evidence of local disease in 2.

The treatment approach in these cases was the same as the one outlined for the previously discussed group, as far as dosage was concerned, while the field arrangement was adjusted to the needs of the individual case. Table VIII shows the poor results obtained in this group. All patients died within 13 months after completion of radiation therapy. Their average survival time was 7½ months, which is not much better than in patients who do not receive any type of treatment, be it surgery or radiation therapy. While the group of patients is small, the trend indicates that the outlook for a disease, which is obviously inoperable, does not improve by attempts to remove "the bulk of the tumor for palliation" even if this procedure is followed by immediate and definitive radiation therapy. The cutting through the cancer at the time of surgery apparently spreads the disease more readily; all of these patients died of generalized metastases. A comparison of the 95 patients in the group found inoperable at thoracotomy and the 20 patients in this group is shown in Table IX. In the group of patients treated by radiation therapy alone after an exploratory thoracotomy had shown the tumor to be nonresectable, 50 patients or 52.6 per cent out of 95 were alive after 13 months, while in the patients who underwent an incomplete removal of the tumor with subsequent radiation therapy, none survived longer than 13 months.

Table IX

COMPARISON OF THE SURVIVAL RATE OF 95 PATIENTS WITH UNRESECTABLE CARCINOMA OF THE LUNG AT THORACOTOMY AND 20 PATIENTS WITH AN INCOMPLETE SURGICAL PROCEDURE

Total no. of patients treated with full course of radiation therapy after exploratory thoracotomy	95	Total no. of patients treated with full course of radiation therapy after lobectomy or pneumonectomy	20
Survived 13 months and longer	50	Survived 13 months and longer	0

SUMMARY

Two groups of patients with inoperable lung lesions are discussed. One group was treated by radiation therapy because the tumor was found to be inoperable at surgery. In the second group, part of the tumor was left behind, or cut through, at the time of lobectomy or pneumonectomy, which was followed by radiation therapy. All patients were treated with 5,000 rads given in a period of 5 weeks with a 2 million volt roentgen ray unit. In the latter of these two groups some patients experienced symptomatic relief, but there was no significant increase in the life expectancy when compared with the average survival rate in untreated patients. This seems to be an indication that a surgical procedure, carried out in spite of inoperable disease, decreases the life expectation of the patient even when radiation therapy is added. On the other hand, in the patients who were treated by external irradiation alone after an exploratory thoracotomy had proved the disease to be unresectable, therapy resulted in gratifying symptomatic relief and in encouraging 1 to 5 year survival rates. These were 57.9 per cent for 1 year, 27.3 per cent for 2 years, 17.8 per cent for 3 years, 11.5 per cent for 4 years and 7.4 per cent for 5 years. It does not appear possible that such beneficial results can be achieved when the tumor is permitted to grow and spread after an unsuccessful exploration, and it is urged that consideration be given to a well planned radiation therapy program immediately after an exploratory thoracotomy.

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FEVER AS A COMPLICATION OF RADIATION THERAPY FOR CARCINOMA OF THE CERVIX*

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DURING radiation therapy of carcinoma of the cervix, fever can be an ominous indication of impending trouble for the patient. This may be expressed as immediate morbidity or it may be manifested by failure of the patient to respond to treatment, that is, the fever may indicate an unfavorable prognosis.

In order to learn more about the nature and prognostic implications of fever encountered during irradiation for cervical cancer, the records of all patients who received primary radiation therapy at the Mayo Clinic from 1940 to 1953, inclusive, were reviewed. Of these patients, 1,666 altogether, 260 experienced fevers higher than 100° F., measured orally, while undergoing radiation therapy. This is an incidence of 15.6 per cent. The incidence in different years varied from a low of 9 per cent to a high of 22 per cent. The occurrence of fever increased in direct proportion to the advancement of the disease. For Stages 0 to 1, grouped together, the incidence was 7.8 per cent, for Stage 2, 9.6 per cent, for Stage 3, 20.3 per cent, and for Stage 4, 24.6 per cent.

For this study, an increase in body temperature was not considered significant unless it rose above 100° F., orally.

Often, the etiology of fever in a patient undergoing radiation therapy may be difficult to determine, for there may be no findings other than the fever. However, the treatment procedure could account for the occurrence of fever in several ways. Considering that the carcinoma is so frequently the site of infection, intracavitary radiation may precipitate fever by exacerbating a quiescent infection, that is, by spreading the inflammatory process locally or even generally. In the course of manipulation necessary for radium applications, it is inevitable that new pathways may be opened up to the spread of infection; in fact, a new infection may be introduced into the pelvis during the procedure. Perhaps, also, high intensity radiation *per se* may cause a quiescent salpingitis to flare up. In addition, the tenuous barriers surrounding regions of malignant necrosis within the pelvic soft tissues may be broken down, permitting the localized dissemination of necrotic neoplasm which, through toxic reactions, can produce sudden acute fever.

For our patients who had significant fever, many different causes were found (Table 1). No specific etiologic factor to account for fever could be determined for 57.3 per cent of the cases, although my clinical impression was that the basis of fever in many of these cases was local dissemination of necrotic material within the pelvic tissues and subsequent toxic reaction. In 21.2 per cent of the patients who developed significant fever, pelvic inflammatory disease was determined to be the cause. "Pelvic inflammatory disease" is a fairly broad term which is here defined to include any nonspecific inflammatory process involving tissues of the pelvis, except for tissues in the uterus, cervix, and vagina. It may be manifested only by tenderness to abdominal palpation (often rebound tenderness) or, at the other extreme, by a definite pelvic abscess which usually resolves without further complication but which may point and drain spontaneously via the rectum, bladder, or vagina, or into the abdominal cavity, resulting in generalized peritonitis.

Local infection was responsible for fever

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* Presented at the Forty-sixth Annual Meeting of the American Radium Society, White Sulphur Springs, West Virginia, April 13–16, 1964.

Table I

ETIOLOGY OF FEVER

Stage	No. of Cases	Causes of Fever				
		Undetermined	Pelvic Inflammatory Disease	Local Infection	Pyometra	Other
0 and 1	16*	10	4	0	0	Severe diarrhea (1); abortion (1)
2	58	36	16	0	3	Peritonitis (2); acute peri-appendicitis (1)
3	116	70	23	3	7	Peritonitis (3); pyogenic cystitis (2); pyelonephritis (2); pneumonia (1); femoral thrombophlebitis (1); influenza (1); vulvar abscess (1); pulmonary embolus (1); acute infectious arthritis (1)
4	70	33	12	15	1	Pyogenic cystitis (3); luetic gastric crisis (1); renal calculus (1); acute radiation cystitis (1); uremia (1); pleurisy (1); femoral thrombophlebitis (1)
Totals	260	149	55	18	11	27
Per Cent		57.3	21.2	6.9	4.2	10.4

*Only 2 were Stage 0.

in 6.9 per cent of patients. Significant local infection is usually encountered in the more advanced stages of cervical cancer. Infection of the tumor occurs sooner or later by reason of its situation where it is in contact with the vaginal bacterial flora. Several factors contribute to tumor infection: ulcerations caused by minor trauma, small necrotic lesions due to defective blood supply, and fissures of the irregular surface of the enlarging tumor, all of which afford excellent soil for bacterial growth.

To determine whether fever affects prognosis, the case records of the 260 febrile patients were studied according to stage of disease and duration of fever. Survival of patients in this group was compared with that of all patients with cancer of the cervix. It became apparent that the prognosis worsens as the duration of fever increases. If fever lasted no more than 7 days (either continuous or intermittent), the percentage of patients who survived for 5 years was 41.2 per cent; if fever persisted for more than 7 days, the percentage was reduced to 25.8 per cent. The over-all survival for all patients who developed fever was 37.3 per cent. This is significantly less than the 5 year survival rate for all patients treated with radiation for cancer of the cervix at the Mayo Clinic during the same period (51.6 per cent). The details of survival data are presented in Table II.

That the prognosis is worsened for patients who develop fever is not an unexpected finding, because other therapists have made the same observation. At Roswell Park Memorial Institute in Buffalo, New York, the 5 year cure rate was 19 per cent for patients treated from 1920 through 1953, who had fever of 101° F. or higher, while for those whose temperatures remained below 101°, the 5 year cure rate was 41 per cent.[3] Similar findings were reported by Goldscheider[2] for the Marie Curie Hospital in London, England, for patients treated from 1925 through 1934. She showed that the 5 year cure rate for patients whose temperature reached 100° F. or more was 12 per cent, while for patients whose temperature remained below 100° the cure rate was 52 per cent. Also at Radiumhemmet in Stockholm, 22 per cent of "infected" patients (1936 through 1945) survived 5 years, while 62 per cent of noninfected patients did so.[4]

Further analysis of the problem of fever in our patients included study from the standpoint of etiology and its relation to survival. The results of this analysis are given in Table III. It is interesting that there is practically no difference in the 5 year survival of those patients whose fever was of unknown etiology and of those whose fever was caused by pelvic inflammatory disease. Local infection seems to signify a more serious prognosis; however, local infection, as a cause of significant fever, was present only in the more advanced stages of the disease. Included among the 27 patients who had "other" causes of fever were 5 patients in whom generalized peritonitis developed; only 1 of these patients survived for 5 years.

When a patient has fever, it may be necessary to temporarily interrupt or even abandon the planned course of radiation therapy. Modified or incomplete treatment might in itself be a factor in reducing the number of patients who survive 5 years. There were 48 patients whose course of treatment was interrupted for 10 days or more or was completely abandoned. Seventeen of these patients (35.4 per cent) lived 5 years or longer. This is only slightly lower than the survival rate for all patients who developed fever (37.3 per cent), and would tend to indicate that interruption of treatment *per se* need not be a critical factor so far as prognosis is concerned.

Immediate mortality among patients who developed significant fever was very low—involving only 2 patients. The 2 patients who died both had generalized peritonitis; 1 died 33 days and the other 40 days after radiation therapy was begun. One of these patients had a Stage 2 lesion which was a Grade 1 adenocarcinoma, and the other had a Stage 3 lesion which was a Grade III squamous cell carcinoma.

The pathologic diagnosis of the carcinomas for those patients who had fever was squamous cell carcinoma for 234 patients (90.0 per cent) and adenocarcinoma (including 2 adenoacanthomas) for 26 patients. Of those with squamous cell carcinoma, 89 patients (38.0 per cent) survived for 5 years, and of those with adeno-

TABLE II

SURVIVAL ACCORDING TO STAGE OF LESION AND DURATION OF FEVER

Stage	Fever for 7 Days or Less			Fever More Than 7 Days			Fever, All Cases			All Patients with Carcinoma of Cervix
	No. of Patients	Survived 5 Years		No. of Patients	Survived 5 Years		No. of Patients	Survived 5 Years		5 Years
		No.	Per cent		No.	Per cent		No.	Per cent	Per cent
0 and 1	15	11	73.3	1	1	100.0	16	12	75.0	87.0
2	43	26	60.5	15	6	40.0	58	32	55.2	67.8
3	85	36	42.4	31	7	22.6	116	43	37.1	51.3
4	51	7	13.7	19	3	15.8	70	10	14.3	18.6
Totals	194	80	41.2	66	17	25.8	260	97	37.3	51.6

carcinoma, 8 patients (30.8 per cent) survived for 5 years.

It would be well to review briefly the technique of radiation therapy for carcinoma of the cervix as employed at the Mayo Clinic to permit more adequate assessment of possible relations between the therapy and the febrile reactions. A detailed description of our technique has been published.[1] The unit of radium treatment is the 50 mg. radium tube filtered with 1 mm. of platinum. The active length of the tube is 11.7 mm.; the over-all length is 19 mm. and the diameter is 4.0 mm. Radium treatments are given twice weekly for 3 to 4 weeks. Hospitalization is usually necessary only on the day and night of treatment. An effort is made to obtain homogeneous irradiation along the entire birth canal. The knee-chest position for the patient is used during placement of radium, and no anesthetic is employed. The 50 mg. radium tube is introduced into the distal portion of the cervical canal, that is, near the cervical os, and left for 10 to 14 hours for each of the first two treatments—the posterior vaginal wall is pushed well away from the radium with packing to secure protection of the rectum. In the third and fourth treatments, also 10 to 14 hours each, the tube is placed in the deeper portions of the cervical canal. At the fifth treatment, a tandem is introduced into the uterine cavity, two 50 mg. tubes being used for 20 to 24 hours. More recently, the tandem has been replaced by a single linear-source tube of similar dimensions. In the last three treatments, radium is placed in the vaginal vault, the 50 mg. tube being encased in a plastic cylinder of appropriate size; but the cylinder most frequently used has a wall thickness of 1 cm. and is first placed transversely across the face of the cervix, then in the right side of the vaginal fornix, and finally in the left side of the vaginal fornix. Time of treatment ranges from 10 to 14 hours in each position.

Thus, a complete course of treatment for a small lesion in a patient with a small vaginal cavity would total around 5,500 mg. hours in 3½ weeks; a more advanced carcinoma would receive about 7,300 mg. hours. With full dosage, point A of a large tumor would receive at least 7,000 gamma r and point B would receive at least 2,000 gamma r. The course of radium therapy as described is for the average or typical carcinoma. Atypical lesions may be treated with variations: for instance, for a large exophytic tumor, one or more insertions of the radium tube into the tumor mass may be used to shrink it before proceeding with the usual course of treatment; for a lesion with considerable involvement of the vaginal wall, local applications of gamma-ray plaques may be used in addition to the usual course of treatment; and, of course, for a far-advanced tumor, individualized variations from the usual course of treatment may be used.

Table III

SURVIVAL ACCORDING TO ETIOLOGY OF FEVER

Etiology of Fever	No. of Patients	Lived 5 or More Years	
		No.	Per cent
Undetermined	149	60	40.3
Pelvic Inflammatory Disease	55	22	40.0
Local Infection	18	2	11.1
Pyometra	11	5	45.4
Other	27	8	29.6
Totals	260	97	37.3

Roentgen therapy during the earlier years of this study was administered for 4 days immediately after completion of the course of radium treatments. Two hundred to 250 kv. peak radiation was employed with a half value layer of from 1.2 to 1.5 mm. of copper. Treatment was administered to the entire pelvis through two anterior and two posterior ports. A single port was treated each day to a complete dosage of 550 r in air. Occasionally, lateral pelvic ports were also used. During the final 3 years covered by the study, the technique of roentgen therapy was modified so that daily treatments were administered concurrently with radium treatments. Treatment was given on alternate days through the anterior and posterior ports, usually 200 r in air, until a total dose of 2,000 to 2,500 r per port had been given. There was a 4 cm. midline separation between the two anterior and two posterior fields.

Approximately three-fourths of the patients who had significant fevers experienced the onset of fever after the placement of radium. The fever developed in 38 per cent of patients during one of the cervical applications, in 24 per cent of patients during the intrauterine application, and in 12 per cent during one of the vaginal treatments. In 26 per cent of the patients, there was no apparent relationship to any of the radium applications, but in most of these cases the fever was already present when the patient was initially admitted.

The occurrence of fever immediately after an application of radium in nearly three-fourths of patients seems to indicate more than a casual relationship. The manipulation of pelvic structures attending placement of the radium may be the major factor. Such manipulation may stir up a quiescent inflammatory process by opening up new pathways for spread of infection or by permitting pelvic dissemination of necrotic tumor. A toxic reaction to such necrotic material can produce sudden acute fever.

It has long been thought that some action of ionizing radiation itself can exacerbate a quiescent pelvic inflammation. I had hoped that this study might shed light in indicating whether this theory is valid. However, no convincing cases were found to indicate that radiation effects *per se* were the primary cause of fever. On the other hand, it was impossible to completely rule out radiation effects as possible contributing factors in some of our cases.

The treatment for fever depends on the etiology. For those cases due to pelvic inflammatory disease or of unknown etiology, absolute rest in bed is the most important single treatment measure. The pelvic contents should be disturbed as little as possible, which means that pelvic examinations must not be done oftener than absolutely necessary. Among our patients, the fever appeared to subside sooner and was more likely to remain subsided if rest in bed was enforced and if repeated pelvic examinations were not performed.

During the period covered by this study, many antibiotic drugs became available. Most of them were employed, but their use did not appear to have decreased the average duration of fever or to have increased the average 5 year survival. Of course, this does not mean that the antibiotic drugs were useless in treatment for specific cases of febrile illness. It is probable that the antibiotics were helpful in preventing more widespread dissemination of pelvic infection. On this basis we have continued to use the broad-spectrum antibiotics.

Local infection, if present in significant degree, is usually apparent at the time of the initial pretreatment examination. Important clues to the presence of both local infection and pelvic inflammation include ulcerations, foul vaginal discharge, and tenderness. Tender adnexal masses and tenderness of the cervix are more suggestive of an inflammatory reaction or abscess than of tumor which is usually nontender. When any of these indications of inflammation or infection are present, it is all the more important that radium therapy be administered cautiously, with minimal manipulation, and that it be given in small doses to limited areas at each application. If fever occurs, radiation therapy should be discontinued and treatment for the fever instituted as already described.

Pyometra with retention of secretions should be treated with drainage. Spontaneous drainage may be accomplished by merely passing a sound into the uterus. If this fails, a sterile rubber urinary catheter may be inserted into the uterus. The end of the catheter is lowered and secretions are drained into a basin. If the secretions are too viscid to pass through the catheter, a few cubic centimeters of aqueous metaphen

(1:2,500) are poured into the catheter and allowed to flow by gravity into the uterine cavity. The tube is then lowered and the uterus emptied. This irrigation process is repeated several times until the solution returns clear. Finally, a small amount of metaphen solution is introduced into the uterus and the catheter withdrawn so that the solution is retained in the uterus. Irrigations are repeated daily until symptoms subside.

Whenever a patient has significant fever, whatever the cause, it is prudent to discontinue radiation therapy until the fever subsides. There is considerable risk of precipitating a second febrile episode when radium therapy is reinstituted, particularly if the fever was caused by spread of infection, by inflammation, or by a toxic reaction within the pelvis. If a second severe febrile illness occurs, it would generally be wise to abandon further radium therapy. However, if the patient's general condition permits, the course of external irradiation may usually be safely completed.

For the less common causes of fever complicating radiation therapy of cancer of the cervix (Table I), specific treatment is indicated. Details of such treatment need not be enumerated here.

SUMMARY AND CONCLUSIONS

A review has been made of 260 cases of significant fever (over 100° F., orally) which occurred during radiation therapy of 1,666 patients who had carcinoma of the cervix. This is an incidence of 15.6 per cent. The majority of fevers were of undetermined etiology (57 per cent) or due to pelvic inflammatory disease (21 per cent). Significant fever appears to worsen the prognosis as evidenced by a 5 year survival rate for these patients of 37.3 per cent as compared with 51.6 per cent for all radiation treated patients with carcinoma of the cervix. Also, the prognosis becomes still poorer for those patients who experience more prolonged febrile episodes. The 5 year survival was reduced to 25.8 per cent if the total period of fever exceeded 7 days.

In most patients the factors which precipitated fever were very probably trauma and manipulation incident to placement of the radium, which cause breakdown of the barriers holding in check an existing infection or inflammatory process or the cancer itself. Obviously then, it is extremely important, in the radium therapy of cervical carcinoma, that efforts be made to refine treatment technique to reduce manipulation and trauma to a minimum.

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AN APPRAISAL OF RADIOACTIVE THERAPEUTIC LYMPHOGRAPHY*

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THE technique of injecting radiopaque agents directly into a lymph vessel has stimulated considerable interest and study of the human lymphatic system. Diagnostic examinations suggested the feasibility of this method of injecting drugs into the lymph vessels and lymph nodes. Preliminary studies have been reported in this country and Europe. Jackson *et al.*[5] treated 9 patients with chemotherapeutic agents by intralymphatic infusion. One patient showed regression of disease but a major disadvantage was that the drugs were not readily soluble in an oily vehicle. Others,[9] using a physiologic solution, have noted systemic effects of the drugs, still in an active form, on the hematopoietic tissues. Jantet[7] approached the problem by injecting radioactive colloidal gold intralymphatically. He believed that this was more practical and favored its use for prophylactic irradiation of the lymphatic system before clinically detectable metastases occurred. Recently, radioactive I^{131} bound to the poppy seed oil (ethiodol), commonly used in diagnostic lymphography, has become available for investigative use. Seitzman *et al.*,[12] using I^{131} ethiodol, demonstrated a uniform assay of radioactivity to the retroperitoneal lymph nodes without significant radioactivity in any other tissue.

This appraisal of radioactive lymphography is based on the use of I^{131} ethiodol in humans and animals. Although it is not the ideal agent, the author preferred it because of previous experience with plain ethiodol in 111 patients for diagnostic studies. Fifty-one patients received the radioactive, radiopaque oil (Table I). Animal experiments were both short and long term, but only findings related to the appraisal are presented here. Through this combined approach, it is hoped that a proper evaluation of therapeutic lymphography can be made.

TABLE I

PATIENTS RECEIVING I^{131} ETHIODOL LYMPHOGRAPHY WITHOUT COMPLICATIONS (DOSE RANGE, 8–35 MC)

		No. of Cases
Pelvic cancers		38
a. Cervix uteri (25)	e. Corpus uteri	
b. Vulva (5)	f. Anus	
c. Testicle (3)	g. Urethra	
d. Fallopian tube	h. Penis	
Lymphomas		8
a. Hodgkin's disease (5)		
b. Lymphosarcoma (2)		
c. Reticulum cell sarcoma (1)		
Retroperitoneal tumors		3
a. Fibrosarcoma		
b. Liposarcoma		
c. Pancreatic carcinoma		
Miscellaneous		2
a. Epidermoid carcinoma of left buttock (with retroperitoneal metastases)		
b. Undifferentiated carcinoma (neck and left axilla)		
Total		51

THE PRIMARY PELVIC LYMPHATIC SYSTEM AND A CANCEROCIDAL DOSE

The technique of injecting anticancer drugs or radioactive isotopes directly into a lymph vessel must be capable of delivering these agents to the lymph node region involved by the disease. It would be of little value if an important group were missed while lymph nodes not of primary importance were injected. Since lymphangiogra-

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phy is most easily performed via the lymph vessels of the dorsal aspect of the feet, comment is made concerning the inguinal, pelvic and periaortic lymph nodes which are readily filled by this route of administration. Earlier investigators[1] concluded that important primary lymph nodes, *i.e.*, the obturator and internal iliac lymph nodes, were not reached or visualized by this method. However, Herman *et al.*[4] have recently reported an excellent clinical roentgen anatomy study of the iliopelvic-aortic lymphatic system in 20 normal subjects. All known iliac pelvic lymph nodes were routinely opacified. It was emphasized that primary lymphatic drainage from the pelvic organs was demonstrated by lymphography. Herman *et al.* also clarified the discrepancies in terminology among surgeons, anatomists and roentgenologists and advocated that Rouvière's[10] earlier anatomic studies and nomenclature be adopted.

In the present series, 12 patients with gynecologic cancer were subjected to lymphadenectomies, 2 to 4 weeks following radioactive lymphography (Fig. 1). Out of 8 pelvic dissections for carcinoma of the cervix, only 2 were considered to be nearly complete. Figure 2 shows the residual lymph node tissue in one of the patients following lymphadenectomy. All lymph nodes which were removed contained the radioactive, radiopaque material. In 4 radical inguinal dissections for vulvar carcinoma, the lymph nodes were more completely removed. The surgical specimens showed that 1 or 2 very small lymph nodes were occasionally found that did not contain the radioactive material. These small inguinal lymph nodes were always free of disease even when other lymph nodes were positive for malignancy. Jacobsson and Johnansson,[6] and Malek *et al.*[8] believe that these few lymph nodes belong to the lesser saphenous system. To inject these lymph nodes, use of a lymph vessel in the Achilles region of the foot would be necessary, rather than the usual dorsal site.

In the 12 gynecologic cancer patients, we not only evaluated the completeness of dissection and the anatomy of the pelvic lymph node system, but also computed the radioactivity absorbed by individual lymph nodes. One hundred and eighteen lymph

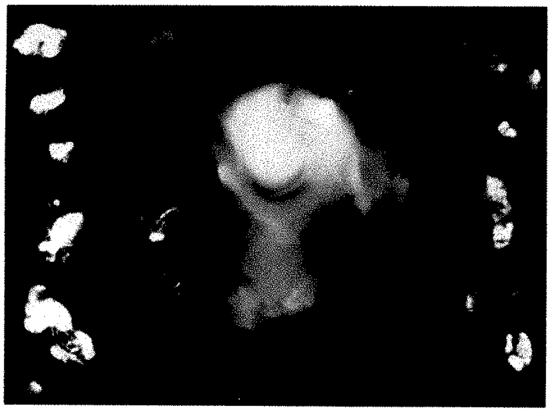

FIG. 1. Roentgenogram obtained of surgical specimen from carcinoma of cervix treated by Wertheim hysterectomy with lymph node dissection (15 days after 12 mc of I^{131} ethiodol lymphography). A mean dose of 14,500 beta rads was absorbed by the lymph nodes. Histologically, the lymph nodes were negative.

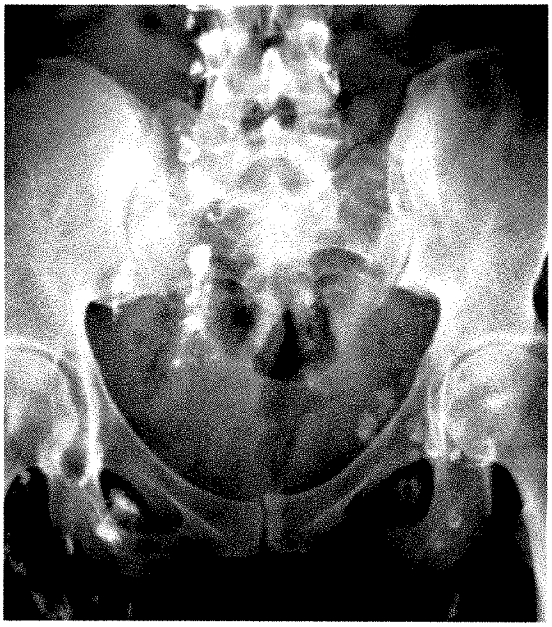

FIG. 2. Pelvic roentgenogram of patient treated by Wertheim hysterectomy and lymph node dissection reveals residual pelvic lymph nodes (see Fig. 1).

TABLE II

118 LYMPH NODES SURGICALLY REMOVED FROM 12 GYNECOLOGIC CANCER PATIENTS, STUDIED TO DETERMINE AMOUNT OF BETA RADIOACTIVITY ABSORBED (SEE TEXT)

No. Studied	Lymph Node Location	Beta Ray Dose (rads)	Mean Dose (rads)
45	External iliac	1,100–36,000	14,311
31	Obturator	2,000–38,000	14,666
20	Internal iliac	2,000–25,000	11,744
22	Inguinal	600–29,000	10,711

nodes were weighed after removal and a scintillation well counter was used to determine the remaining radioactivity. Proper calculations were made so as to express the dose in rads to total decay *in vivo* for each node.* In Table II the beta ray dose range and mean values for the 118 lymph nodes are summarized. There were only 8 lymph nodes that received less than 4,000 rads and half of these were in a single patient. This patient received the lowest dose, 9 mc of I^{131} ethiodol given in 18 cc. of oil. The highest dose was 20 mc of I^{131} ethiodol given in 12 cc. of oil. A more detailed analysis of the beta ray dosage to the lymph nodes within each pelvic lymph node group will be reported in collaboration with the Department of Gynecology. From the anatomic and surgical studies, it is reasonable to assume that there is good evidence that radioactive lymphangiography will deliver cancerocidal doses to the involved lymph node regions of many pelvic cancers.

INDIVIDUAL LYMPH NODE METASTASIS AND ITS ABSORPTION OF INJECTED ISOTOPE

The second significant factor of therapeutic lymphography is the individual lymph node metastasis, with its capability to absorb and retain the therapeutic material. Figure 3 shows early metastasis in an iliac lymph node from a patient with vulvar cancer, who had had prior diagnostic lymphography. Surrounding the small metastasis are numerous clear spaces representing areas which contained the radiopaque oil but which was dissolved during histologic preparation. It is this proximity of the injected substance to cancer in the lymph node which is important. Since the radiopaque oil remains in the lymphatic system for many months, an appropriately bound radioactive isotope could deliver a radiation

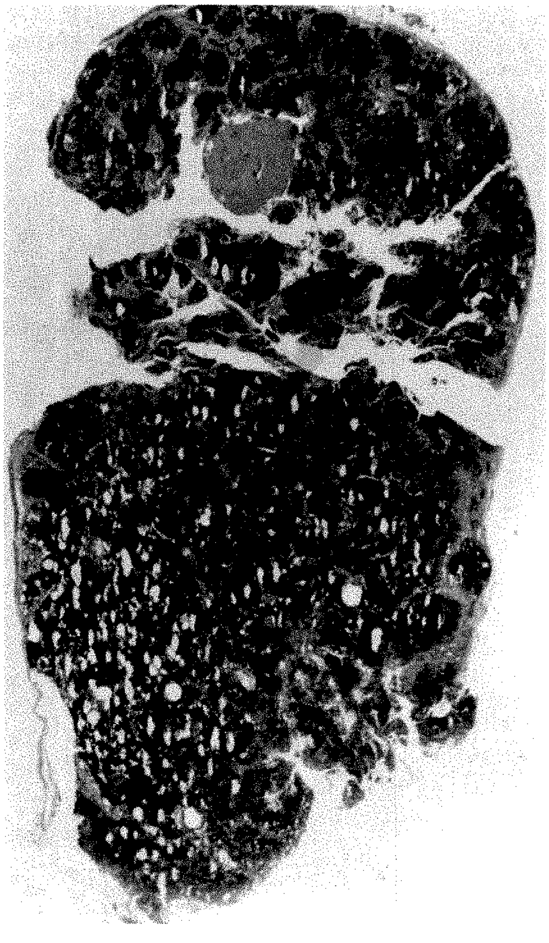

FIG. 3. Photomicrograph shows early metastasis in iliac lymph node from a patient with vulvar cancer. Surrounding the small metastasis are numerous clear spaces representing the nonactive radiopaque oil dissolved during the histologic preparation. This proximity of the injected oil to the cancer in the lymph node is important (×35).

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* The basic formula for addition of beta and gamma ray dosages from internally administered isotopes is $D_{\beta+\gamma} = CT\ (73.8\ \bar{E}_{\beta} + 0.0346\Gamma g)$.[2] Since the contribution of the gamma emission is insignificant because of the small size of the lymph nodes, the absorbed dose in rads was calculated utilizing only the beta emissions. D_{β} (in beta rads to total decay *in vivo*) $= 73.8 \times$ concentration (μc/gm.) $\times 0.187$ ($\bar{E}_{\beta}$ for I^{131}) $\times T$ (effective half life).[12]

dose to the lymph node. Its decay scheme should be such that the dose is delivered locally before degradation of the product occurs and it is released from the lymph node tissue. Thus, depression of the bone marrow and undesirable side effects on surrounding or overlying tissues can be avoided. The I^{131} isotope bound to poppy seed oil (ethiodol) has been used throughout this study, but newer agents may prove more efficacious.

Figure 4 shows the distribution of the I^{131} ethiodol within an inguinal lymph node that is nearly two-thirds replaced by neoplastic tissue. Along one peripheral zone, a moderate amount of remaining lymphoid tissue can be seen, containing clear spaces representing the radiopaque oil areas dissolved during histologic preparation. Near the hilus is a small island of normal lymphoid tissue with clear spaces.

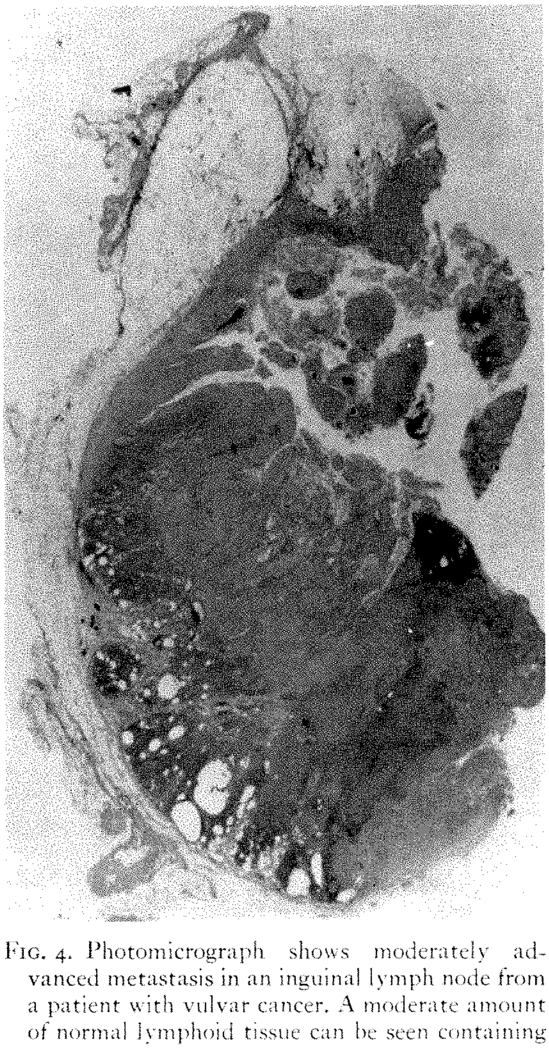

Fig. 4. Photomicrograph shows moderately advanced metastasis in an inguinal lymph node from a patient with vulvar cancer. A moderate amount of normal lymphoid tissue can be seen containing the clear spaces representing the radiopaque oil. On the opposite border is a smaller zone of lymphoid tissue (×35).

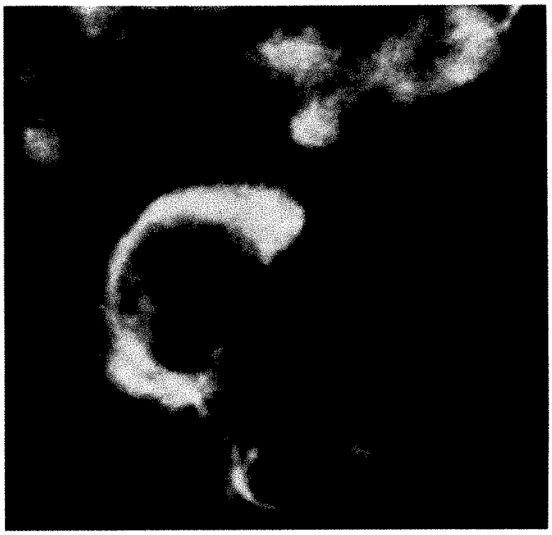

Fig. 5. Roentgenogram of a surgically removed right internal iliac (obturator) lymph node from a patient with carcinoma of the cervix. The metastasis in the lymph node is surrounded by a zone of radiopaque radioactive oil.

Figure 5 is a roentgenogram of a surgically removed right iliac (obturator) lymph node from a patient with carcinoma of the cervix 1 month after the injection of 20 mc of I^{131} ethiodol. The radioactive, radiopaque material can be seen encircling the metastasis. Figure 6 is a photomicrograph of a portion of the same lymph node. Peripherally, the lymphoid tissue with clear spaces can be seen. Next, there is a zone of marked fibrosis and hyaline change. Lastly, the innermost region shows bizarre tumor cells scattered throughout the fibrous reaction.

Almost complete replacement of a lymph node with metastasis was noted in a dog which was studied. A pet black terrier had an epidermoid carcinoma of the left nuchal region, which was removed but a lymph node mass appeared several months later. Radioactive lymphangiography was performed with injection behind the left ear

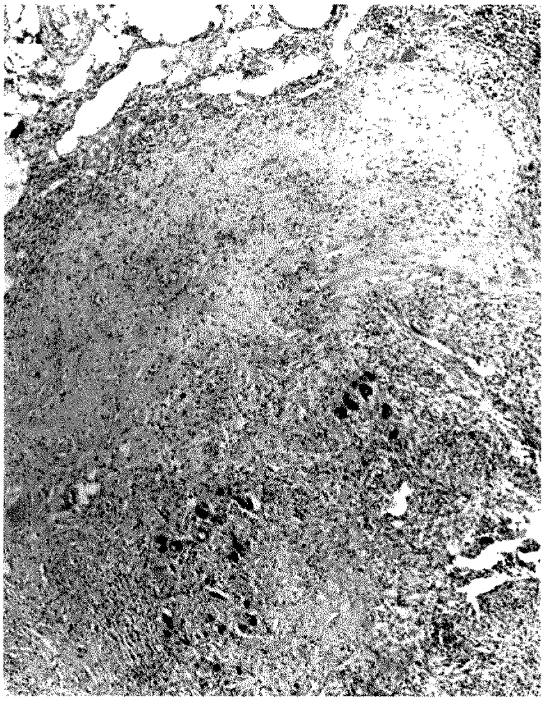

FIG. 6. Photomicrograph of a representative area of the lymph node illustrated in Figure 5. The peripheral portion shows the lymphoid tissue with clear spaces representing radioactive oil. Adjacent to this zone, there is marked fibrotic reaction with isolated tumor cells.

and also into the left paw, after which a large lymph node measuring 5×3×1.5 cm. was removed. An autoradiograph of the sectioned lymph node was made. The same lymph node was photographed to actual size and the negative was accurately superimposed on the autoradiograph. The resulting photograph is shown in Figure 7. The lymph node was entirely replaced by tumor except for a very small rim of lymphoid tissue. The marked radioactivity in that area can readily be seen. Only a very minute amount of radioactivity is present in the tumor substance. This large metastatic lymph node was sampled once in an area of obvious tumor and twice where the small amount of oily medium was present. Scintillation well counting of the samples and subsequent calculations revealed a beta ray absorption of 70 rads, 2,700 rads, and 7,800 rads, respectively.

The foregoing examples have shown the degree of filling that will occur within lymph nodes involved with early and advanced stages of epidermoid carcinoma. Does this same pattern occur with other pathologic conditions? Evidence from a study of 25 lymphoma patients who received radioactive ethiodol and from the medical literature tends to substantiate the impression that lymph nodes involved with a primary process, *e.g.*, the lymphomas, are more likely to fill or absorb the injected material.[3,11,13] A lymph node may be enlarged several times its normal size due to the lymphomatous process and yet nearly adequate distribution of the injected material can be obtained (Fig. 8). A larger amount of material is absorbed for a given weight of lymphomatous lymph node tissue than for metastatic carcinomatous lymph node tissue.

Beside this higher degree of retention, there is a marked biologic effect that can be observed when radioactive I^{131} ethiodol is distributed within the lymphomatous node. Although regression of Hodgkin's disease and lymphosarcomatous inguinal lymph

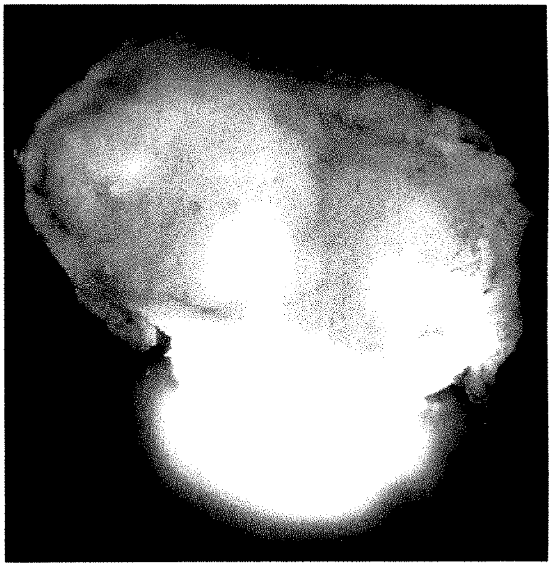

FIG. 7. Photograph obtained by superimposing the actual size negative of a cervical metastatic lymph node (dog) onto the autoradiograph of the lymph node. The distribution of the radioactivity in this advanced metastatic lymph node is clearly illustrated (see text).

nodes has been observed in patients, a controlled experiment showed the following biologic effect. The left hind paw of a dog with malignant canine lymphoma was injected with 9 mc of I^{131} ethiodol. At the same time a similar injection was made into the right hind paw with an equal amount of plain ethiodol. A roentgenogram obtained after the injections showed the lymph nodes symmetrically enlarged bilaterally in the popliteal, pelvic and lower lumbar regions. The dog was observed for 1 month, and then the iliac and popliteal lymph nodes were removed bilaterally for comparison. Figure 9 demonstrates the enlarged right iliac and popliteal lymph nodes with progressive disease. The metastatic involvement in the left iliac and popliteal lymph nodes has completely regressed. These gross changes were confirmed in the histologic sections shown in Figures 10 and 11.

Malignant melanoma lesions of the extremity will metastasize to the regional lymph nodes of the axillary or inguinal region. These lymph nodes can be injected for lymphangiography. Figure 12 shows the left axilla of a 30 year old male patient who had a melanoma of the arm removed 5 years previously. The large axillary lymph node mass shows a moderate amount of radiopaque material. Other authors have described similar findings.[3,13]

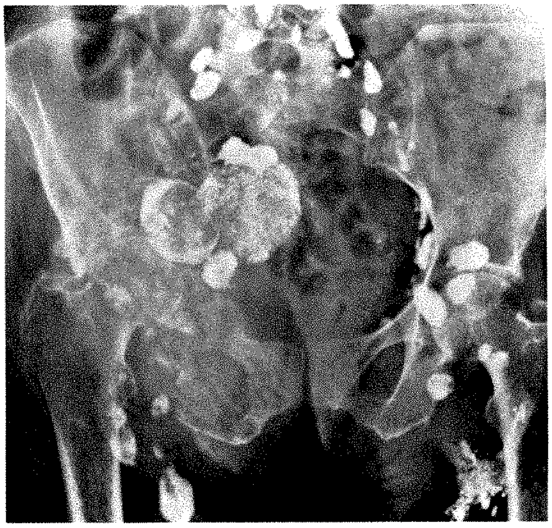

FIG. 8. Pelvic roentgenogram shows marked enlargement of right iliac lymph nodes with invasive destruction of adjacent osseous structures. Inguinal lymph node biopsy showed Hodgkin's disease. There is good filling of Hodgkin's lymph nodes regardless of size.

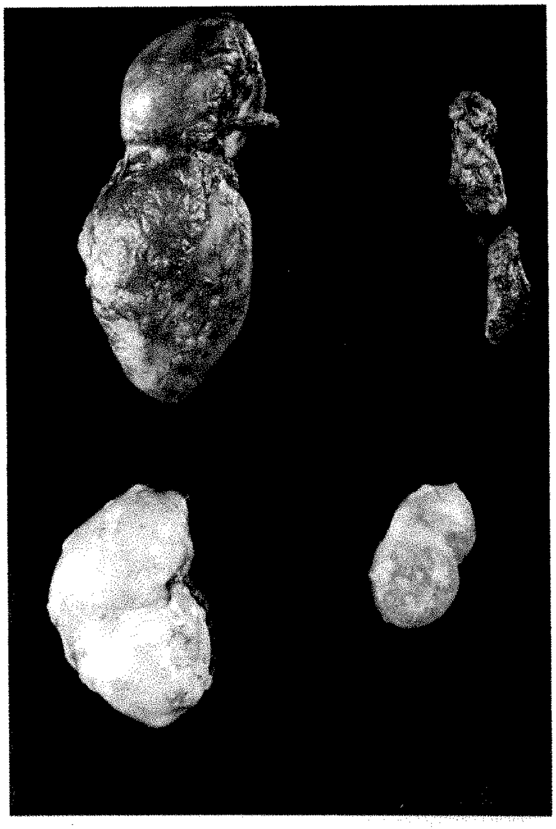

FIG. 9. Photograph of surgically removed iliac and popliteal lymph nodes from a dog with canine lymphoma. One month previously the right lower paw was injected with 5 cc. of nonactive oil (enlarged lymph nodes). The left lower paw was injected simultaneously with 5 cc. of active I^{131} oil (9 mc). These lymph nodes have regressed.

Lymphograms of sarcoidosis reveal diffuse lymph node enlargement simulating the lymphoma pattern. The seminoma lymph nodes are more likely to absorb moderate amounts of material, especially in the early to moderate stages of involvement; however, metastatic teratocarcinoma lymph nodes resemble those of epidermoid carcinoma.

Our observations show that best filling or retention of injected materials can be ex-

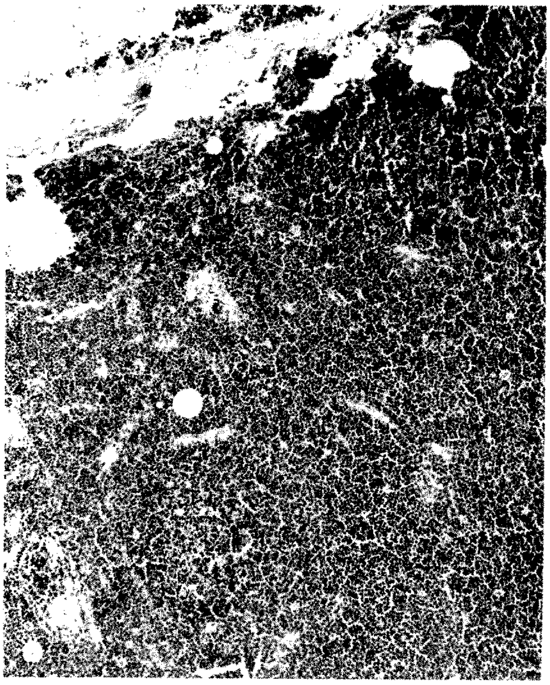

FIG. 10. Photomicrograph of histologic section of one of the enlarged lymph nodes in Figure 9. The lymphomatous cellular proliferation is markedly evident and has caused dispersion of the absorbed oily material (clear spaces) (×80).

←

pected in lymphoma, sarcoid, and seminoma lymph nodes in the order cited. Metastatic melanoma lymph nodes would be intermediate in classification. Advanced metastatic epidermoid carcinoma or teratocarcinoma lymph nodes would fill the least. Of course, if the metastases are very early or minimal, the filling should be adequate and similar in all disease states.

CLINICAL APPLICABILITY OF THERAPEUTIC LYMPHOGRAPHY

Beside the 12 gynecologic patients whose surgically excised lymph nodes were intensively studied, an additional 38 cancer patients had radioactive lymphography (Table I). Because radioactive isotopes can de-

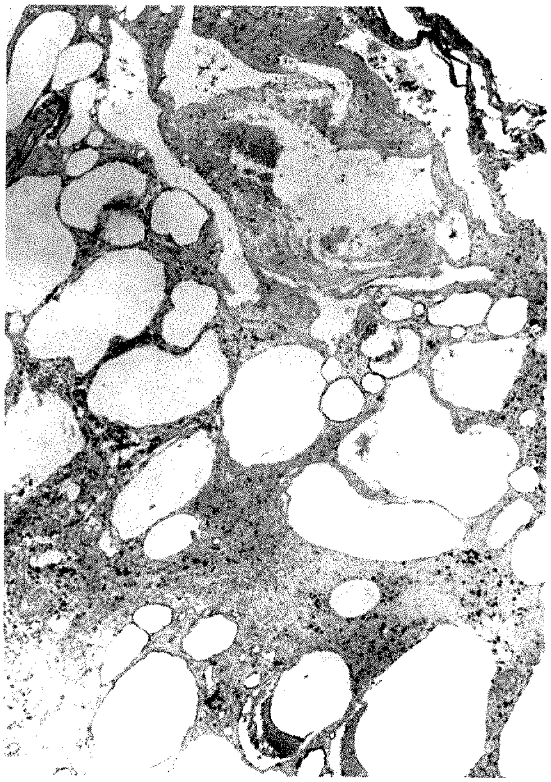

FIG. 11. Photomicrograph of histologic section of one of the regressed lymph nodes in Figure 9. Note marked depletion of lymphomatous cellular proliferation.

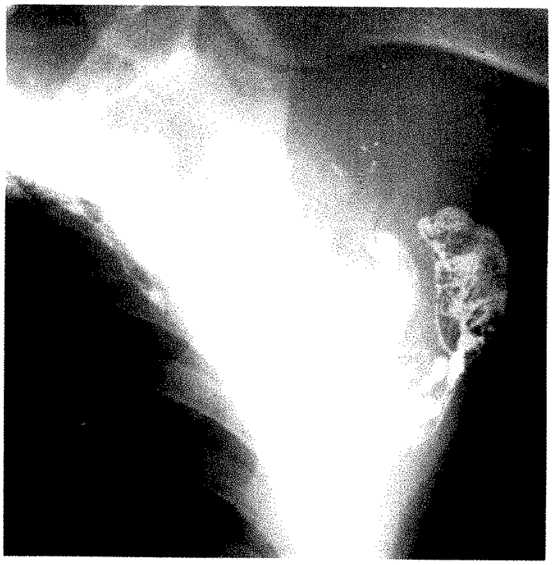

FIG. 12. Left axillary roentgenogram after diagnostic lymphography. This 30 year old male had a melanoma removed from the left arm 4 years previously. This degree of filling of advanced metastatic lymph nodes indicates possible therapeutic use (see text).

liver cancerocidal doses to early cancerous lymph nodes of the inguinal-pelvic-aortic region and adequate complete surgical removal is not always desirable or feasible, radioactive lymphography can be used as a therapeutic adjunct (Fig. 13).

Carcinoma of the cervix, vulva, penis, bladder and prostate involves the lymph node regions discussed. Radioactive lymphography, added to the established surgical and radiotherapeutic management, should help to control the frustrating aspect of lymph node metastases. The following case is presented as an example of the use of radioactive lymphography.

A 70 year old female developed a vaginal lesion 1 year following previous treatment for uterine carcinoma. Biopsy showed that the lymphatic vessels contained neoplastic cells (Fig. 14). The vaginal lesion was treated with a radium needle implant and radioactive lymphography was performed to control the lymph node metastasis. No signs of disease are clinically demonstrable 16 months after the last procedure. At least, injection of radioactive material into the lymphatic system has not hastened the appearance of local or distal metastases.[11]

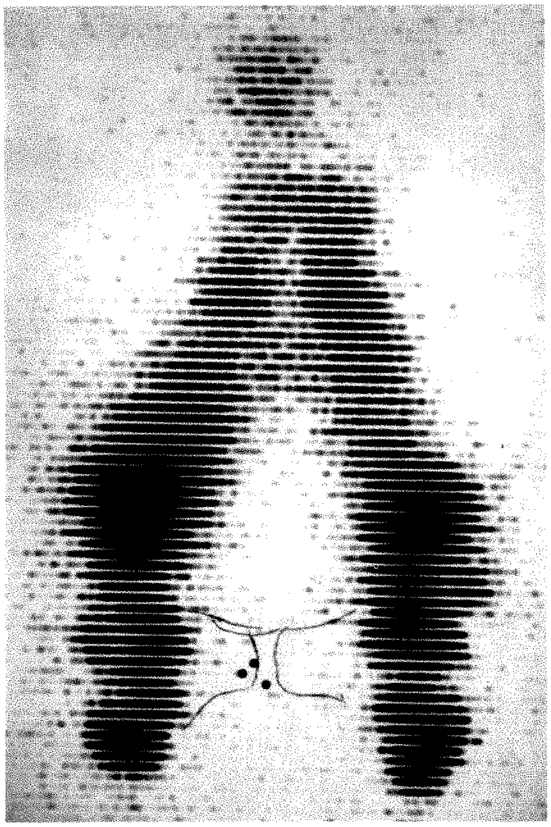

Fig. 13. Photoscan of pelvis and lower abdomen 30 days after 18 mc of I^{131} ethiodol was injected. Therapeutic lymphography was done preoperatively as adjunct to surgery. Because of medical reasons, only bilateral superficial groin dissection was performed for cancer of vulva.

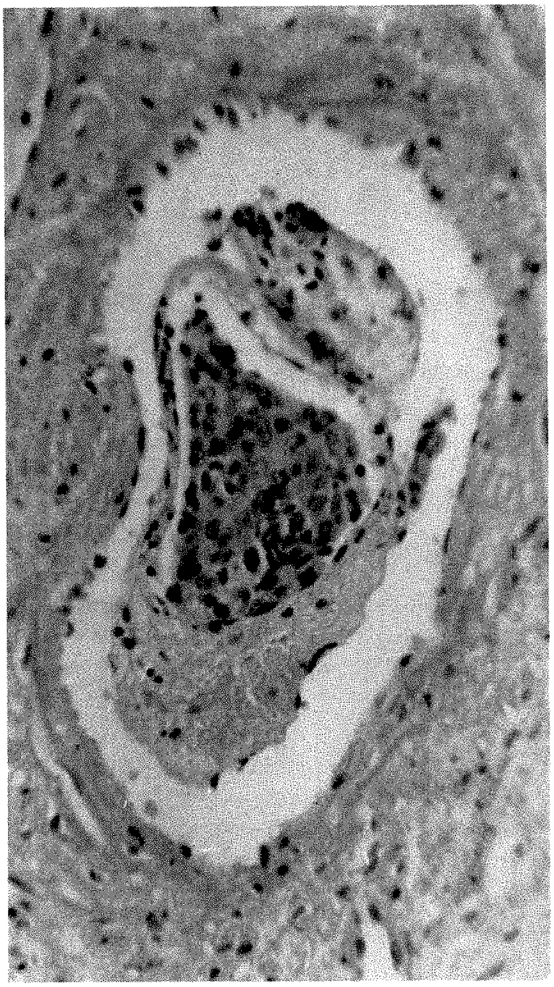

Fig. 14. Photomicrograph shows malignant cells within the lumen of a lymphatic vessel. Biopsy was taken from vaginal recurrence of uterine carcinoma (×175).

Testicular tumors spread primarily to lymph nodes of the periaortic region at the level of the kidney. These lymph nodes may be filled via spermatic cord lymphangiography and/or lower extremity lymphan-

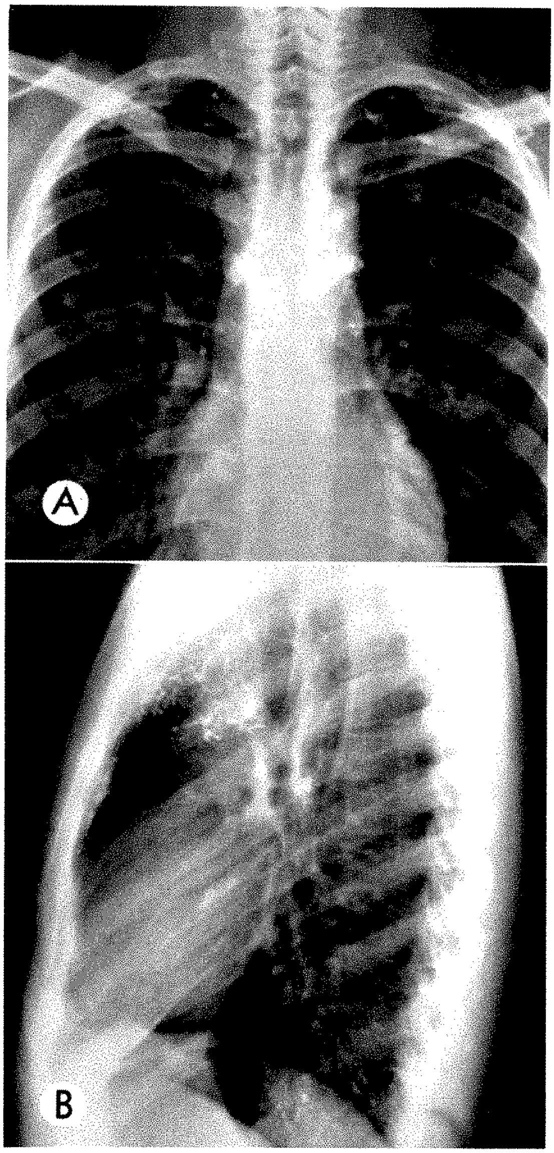

Fig. 15. (*A* and *B*) Anteroposterior and lateral roentgenograms of chest in a 22 year old patient who had a left testicular seminoma. The radiopaque lymph nodes received 21 mc of I^{131} ethiodol via bilateral lower extremity lymphography (see text).

giography. At times excellent distribution of the radioactive isotope is achieved in the potentially malignant pathway. Figure 15, *A* and *B*, demonstrates the additional filling of the internal mammary, supraclavicular, and several mediastinal lymph nodes in a 22 year old patient with seminoma of the left testicle, which was proven at surgery. Lymphangiography made it unnecessary to prophylactically irradiate the mediastinum and supraclavicular regions. In 2 other teratocarcinoma patients, we have found that the metastases caused interference of lymph flow and produced obstruction within the periaortic lymph nodes on the same side as the testicular lesion. Therefore, to benefit teratocarcinoma patients, early prophylactic radioactive lymphography should be performed as soon as the diagnosis is known and should possibly be repeated 6 months later. Since these lesions are only slightly radiosensitive, the high local intense radiation dose in the presence of only a few malignant cells is the only present hopeful treatment.

The lymphoma patient should benefit most favorably for the reasons given. Figure 16 shows a photoscan of a patient who had an early lymphosarcoma of the left inguinal region, proven by biopsy. His entire treatment to date has consisted of radioactive lymphography of both lower extremities. Nearly 9 months have elapsed with no clinical evidence of recurrence at any site.

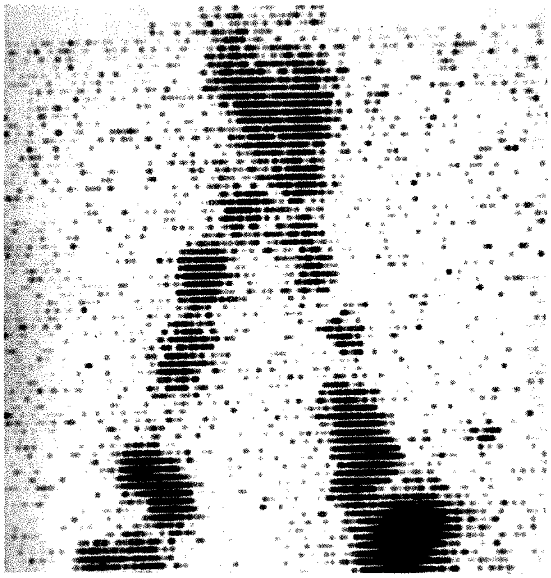

Fig. 16. Photoscan of abdomen and pelvis made 53 days after 25 mc of I^{131} ethiodol. This 45 year old male had early lymphosarcoma of left groin and radioactive lymphography was his only treatment.

In most cases radioactive lymphography can be used as an adjunct to external radiation therapy or chemotherapy, thereby reaching a large number of lymph nodes with less systemic side effects. As stated above, injection of the lower extremities will allow treatment of lymph nodes of the inguinal-pelvic-aortic regions. Although the left supraclavicular lymph nodes can be injected frequently by this route, it is most unusual to fill the greater number of mediastinal and opposite supraclavicular lymph nodes. Axillary and supraclavicular lymph nodes can be reached by using the lymph vessel of the dorsum of the hand. Nevertheless, the mediastinum and neck are best treated by external irradiation. The most serious disadvantage is that the lymphomatous process is a widespread systemic disease and often the lymph node regional anatomy is such that it is impossible to reach certain areas by the conventional hand or foot intralymphatic injection.

Use of the hand site will give adequate filling of the axillary lymph nodes and often of the supraclavicular lymph nodes, but the internal mammary chain is not dependably reached either by the hand or the foot injection. We have had the opportunity to study 15 patients with carcinoma of the breast with diagnostic lymphography, performed chiefly postoperatively. Perhaps, if we could use the procedure preoperatively or at the time of surgery, a technique of injecting the internal mammary chain could be developed.

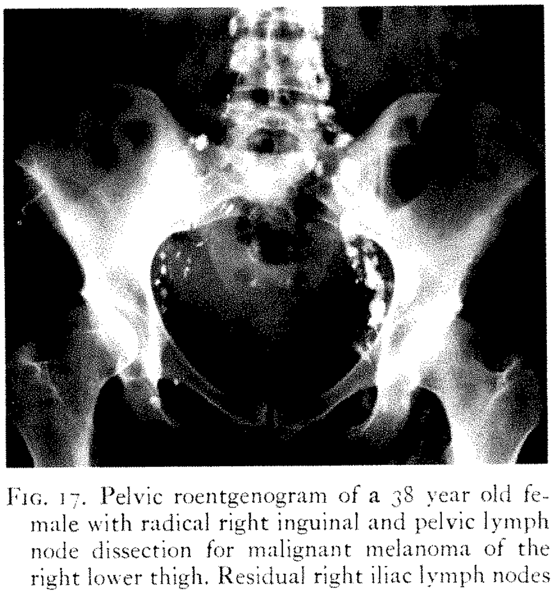

Fig. 17. Pelvic roentgenogram of a 38 year old female with radical right inguinal and pelvic lymph node dissection for malignant melanoma of the right lower thigh. Residual right iliac lymph nodes are seen. When radioactive lymphography is done preoperatively, any early metastases present in residual lymph nodes will be treated.

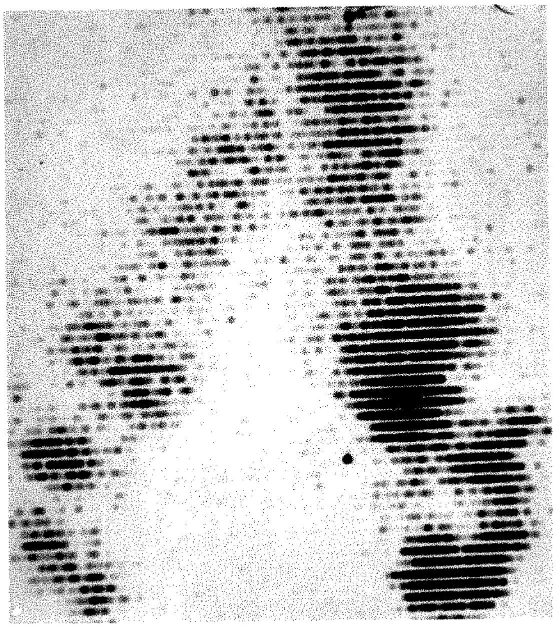

Fig. 18. Photoscan of abdomen and pelvis 37 days after 8 mc of I^{131} ethiodol lymphography. This 68 year old patient was previously operated on for liposarcoma of the left retroperitoneal region.

Patients with malignant melanoma of the lower or upper extremity should benefit from radioactive lymphangiography, especially if done early, prior to radical surgical dissection. Any residual lymph nodes that are not removed will contain the radioactive material (Fig. 17). Epidermoid carcinoma lesions of the extremities and gluteal regions, whether primary or secondary in chronic ulcers, are other indications for radioactive lymphography.

Retroperitoneal tumors are rarer conditions that may respond, but more experience is needed to properly evaluate this group. Figure 18 is a photoscan of a 65 year old male who had a liposarcoma operated on near the left common iliac region. Subsequently, radioactive lymphography was done during his course of external betatron irradiation as an adjunctive measure. At present, 1 year later, he is well and there are no sequelae to the treatment.

Lymph node metastases of the neck are most often due to epidermoid carcinoma and are usually seen in moderately advanced stages. The technique of using a postauricular lymphatic vessel to fill a portion of the cervical lymph nodes is the most difficult intralymphatic injection to do routinely. Most of our attempts have been on outpatients. Whether a prophylactic neck technique could be developed with better sedation and a larger skin incision is difficult to say.

SUMMARY AND CONCLUSIONS

In therapeutic lymphography, the primary growth must metastasize in such a manner that intralymphatic injection can follow the possible spread of neoplastic cells in order to be of significant help. Of the three common sites for injection, lymphangiography of the foot is the easiest to perform. The inguinal, pelvic and aortic lymph nodes reached are those which primarily are involved by cancer of the pelvic organs, the perineum, and the lower extremities. A study of 118 lymph nodes removed from 12 gynecologic cancer patients substantiates the concept that cancerocidal doses can be administered to the important lymph node regions. The possibilities and limitations of using the hand and neck sites for injection are mentioned.

Because distribution of active and nonactive ethiodol is the same, metastatic lymph node absorption was studied in combined diagnostic and therapeutic patients. If metastases are very early or minimal, the absorption of injected radioactive isotope or drug should be adequate and similar for a variety of different cancers. Response will depend upon the sensitivity of the neoplastic cells to the agent which is injected. When metastases are more advanced, lymphomas or primary diseases of the lymph nodes will best absorb or retain the injected material. Epidermoid carcinoma will retain the least amount, when advanced disease is present.

Clinically, radioactive lymphography is employed primarily as an adjunct to established surgical and radiotherapeutic techniques. Preoperative radioactive lymphography has the advantage that unremoved metastatic lymph nodes will most likely have minimal disease and will respond to radioactivity. Prophylactic irradiation of the regional lymphatic system before detectable metastases occur may be the best use.

Further progress in making the method more successful will depend upon the development of a technique for the neck and mediastinum. Newer chemotherapeutic or radiotherapeutic drugs may be more effective in treating more advanced metastatic lymph nodes; however, one must also realize that with this method an appropriately bound medical agent can be introduced into the lymphatic system, and a more prolonged systemic effect can be obtained when the active agent is slowly released by degradation.

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LINEAR ACCELERATOR SUPERVOLTAGE RADIATION THERAPY[*]

CARCINOMA OF THE BLADDER

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THE purpose of this paper is to present our experience with linear accelerator supervoltage roentgen therapy in 196 patients treated in a uniform manner for carcinoma of the bladder.

Radiotherapeutic interest in carcinoma of the bladder stems from the poor survival results following surgical management, particularly in deeply invasive and poorly differentiated neoplasms. Whitmore's[12] 5 year survival results following radical surgery were 47 per cent when no more than superficial muscular invasion had occurred, 17 per cent when deep muscle invasion was demonstrated, 13 per cent when tumor had penetrated to the perivesical fat, and only 3 per cent when either pelvic fixation or lymph node metastases were discovered. In this same report, Whitmore emphasized that the majority of deaths were due to cancer and that one-third of these deaths were directly attributable to sequelae of local pelvic tumor. In addition, there was no significant improvement in the survival rates following introduction of more radical surgical procedures, including pelvic exenteration.

Significant cure rates in bladder carcinoma have not been obtained with 200–300 kv. irradiation.[5] Intracavitary sources were employed with some success during the 1950's, but were of value only for the more superficial lesions.[6] Late complications from the high dose delivered to the mucosa have diminished the enthusiasm for this technique. Interstitial implants have regained popularity with the development of tantalum and iridium wire.[3] The particular advantages of supervoltage radiation therapy should be apparent in the ease of administration of a tumoricidal dose to a large volume (*e.g.*, the entire pelvis), and reflected in improved survival results. Early results from other centers support this thesis.[4,8,10,11]

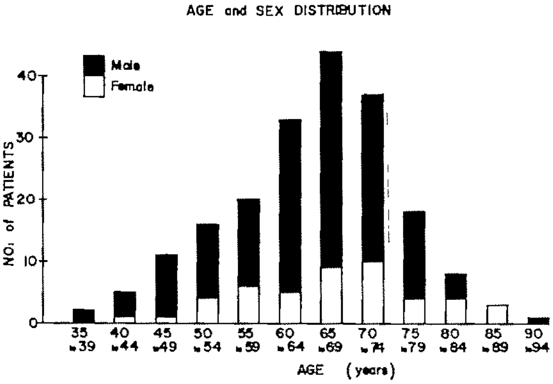

FIG. 1. Age and sex distribution. Median age 66 years. Male:female ratio = 3.2.

STANFORD MATERIAL

One hundred and ninety-six patients with primary bladder cancer have been seen in the Division of Radiotherapy at the Stanford Medical Center since roentgen therapy with the linear accelerator was initiated in January, 1956. All cases have been followed. The median age was 66 years, and the sex ratio (male: female) was 3.2 (Fig. 1). Hematuria was present in all but 40 patients and was the most frequent presenting complaint. It occurred in the same percentage of cases in each stage (Table I). Eighty per cent of tumors were of transitional cell type. Table II shows the treatment undertaken before referral for linear accelerator therapy. As a consequence of prior treatment, the delay before referral was more

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TABLE I

CHIEF COMPLAINT

Hematuria	158
Frequency	29
Cystitis	35
Obstruction	7
Incidental	2
Other	5

Note: Forty of 196 patients had no hematuria.

TABLE III

ONSET OF DISEASE TO START OF TREATMENT

<3 months	33
3 – 5 months	26
6 – 8 months	26
9 –11 months	14
12–17 months	33
18–23 months	12
2 – 3 years	15
>3 years	39

Note: Delay of more than 1 year occurred in 50 per cent of the cases.

than 1 year in half of the patients (Table III). Earlier referral for radiation therapy occurred in advanced cases, and only after surgical procedures had failed. One hundred and ninety-one patients had cystoscopically visible and/or palpable tumor at the time of referral. In the remainder, histologic evidence of incomplete surgical excision was present.

Primary tumor location was as follows: lateral walls—72 cases, trigone—39 cases, floor and neck—21 cases, dome—15 cases, and multiple sites were involved in 18 instances.

These 196 patients have been classified according to the system of Marshall[7] (Table IV). In this system, the histologic appearance is graded I–IV, according to the degree of anaplasia. Anatomic staging is indicated by letter, A, B, C, D. Mucosal involvement is designated Stage A; superficial muscular involvement Stage B_1; deep muscular involvement Stage B_2; penetration through the bladder wall to the perivesical fat Stage C; intrapelvic metastasis Stage D_1; and metastasis beyond the confines of the pelvis Stage D_2. In this retrospective study, it was not always possible to specify the degree of muscle invasion or to know if distant metastases were present. Therefore, the 6 patients believed to be Stage B_1 have been included in the total group of 76 labeled Stage B, and the 54 patients in Stage D can be divided into 27 presumed Stage D_1+, 12 proven Stage D_2+, 15 Stage D not otherwise specified. We have staged prostatic invasion as Stage C.

TABLE II

PREVIOUS TREATMENT

None	9
Transurethral Resection	68
Multiple Transurethral Resections	88
Laparotomy	23
Cystotomy	7
Partial Cystectomy	32
Total Cystectomy	1
Urinary Diversion	10
Roentgen Therapy	1
Other Radiation Therapy	5
No Data	12

TREATMENT PROGRAM

After a complete work-up to determine the extent of disease, each patient is classified by stage. When tumor is confined to the mucosa or superficial muscle, treatment is limited to the bladder. We attempt to deliver a maximum tumor dose of 7,000

TABLE IV

CLASSIFICATION OF PATIENTS

		Stage				No Data	Total
		A	B	C	D		
Grade	I	6/2	1/–	1/–	2/–	—	12
	II	2/1	14/3	5/1	4/4	1/–	35
	III	1/–	29/3	22/4	14/3	—	76
	IV	–/2	13/7	7/–	11/6	–/1	47
No data		3/–	4/2	3/3	7/3	1/2	28
Total		17	76	46	54	5	198

Key ♂/♀.

Note: The 198 cases include 2 patients with metastases to the bladder who were not staged.

rads in 6 to 8 weeks, usually employing a rotational technique (Fig. 2*a*). When it was apparent that treatment was tolerated well, we gradually increased the field size so that now the bladder and regional lymph nodes are treated when deep muscle invasion, serosal involvement or intrapelvic metastases are demonstrated. Usually, a four-field box technique is used in an attempt to perform an *en bloc* radiotherapeutic sterilization (Fig. 2*b*). We have almost always been able to deliver 6,000 rads throughout the pelvis, and an additional 1,000 rads frequently by rotational therapy to the bladder in Stages B and C, at approximately 200 rads per day.

In planning therapy, the bladder is outlined with 50 ml. of a 50 per cent solution of hypaque after introduction of a Foley catheter containing mercury in its balloon. The catheter serves to mark the bladder outlet. Frontal and lateral roentgenograms are obtained with skin markers in place and with barium outlining the rectum and sigmoid. A contour is made with the patient in the treatment position, the bladder tu-

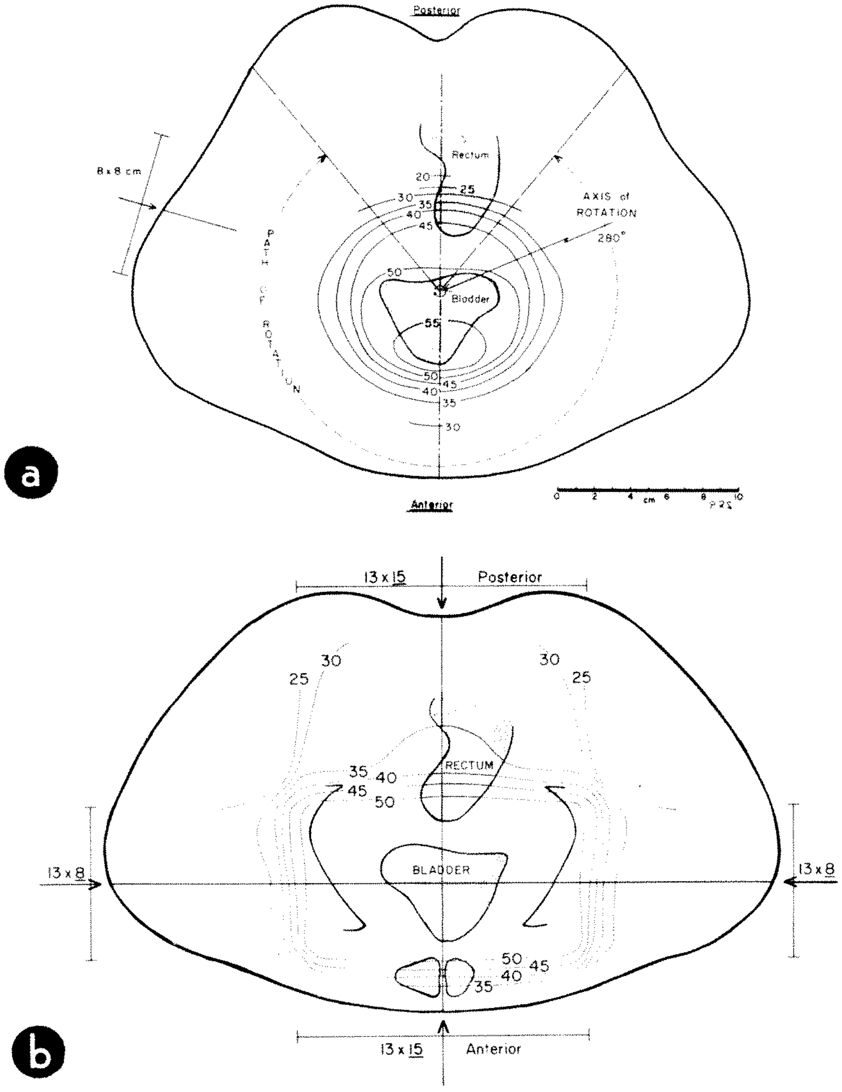

FIG. 2. Isodose patterns for treatment of a standing patient with the 4.8 mev. linear accelerator. (*a*) 280° arc pattern. High dose limited to bladder and perivesical tissues. (*b*) "Box" technique to include bladder and regional lymph nodes.

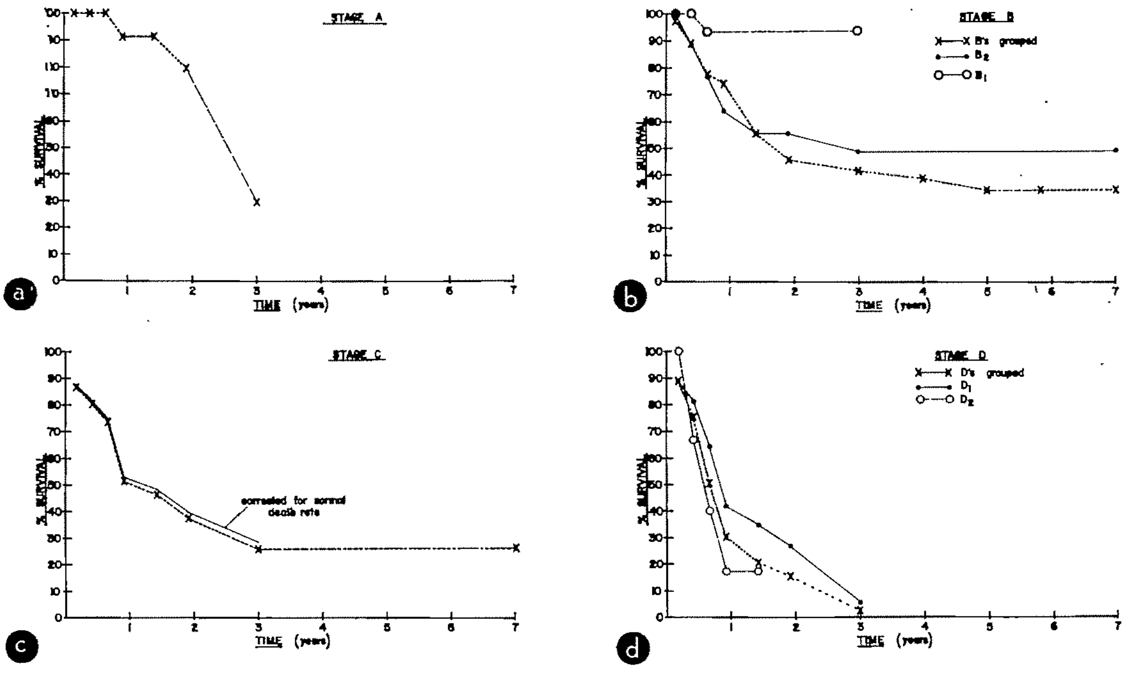

FIG. 3. Berkson-Gage survival curves for (*a*) Stage A, (*b*) Stage B, (*c*) Stage C, and (*d*) Stage D. Note flattening of curves at 3 years, indicating that most deaths had occurred before this time. In *c* the thin line indicates the survival curve when a correction is made for the normal death rate.

mor and other structures are located, and a treatment plan is constructed. Verification roentgenograms are obtained to check each port.

RESULTS

Berkson-Gage survival curves are presented in Figure 3, *a–d*. (These curves are not corrected for the normal death rate and all deaths were scored as due to cancer. The curves would be about 3 per cent higher if corrected.) Seventeen Stage A patients have been treated. Recurrence as well as development of tumor at new sites has occurred despite 7,000 rads administered to the bladder. The break in the curve at 23 months reflects the influence of 2 deaths not due to cancer in a small number of patients eligible for evaluation after this time. The uncorrected 5 year survival rate for the 76 patients in Stage B is 33.5 per cent. The rate falls to 32.2 per cent if the 6 Stage B_1 patients are eliminated. In Stage C (46 cases), the 5 year survival is 25.4 per cent. The uncorrected 3 year survival for all patients in Stage D is 3 per cent.

COMPLICATIONS

In almost all cases, the planned course of therapy was completed. Excluding 9 patients treated with lower doses for palliation, and 2 patients not treated, 1 course was interrupted for intercurrent disease, 1 was interrupted for a treatment complication, and 5 patients required a decrease in the daily tumor dose from 175 to 225 rads per day to 100 to 150 rads per day. In 6 instances, treatment was stopped because of progressive deterioration of the patient in the presence of newly appearing distant metastases.

All complaints have been scored as complications during the course of therapy (Table v). It was not possible to distinguish satisfactorily between complaints existing prior to commencement of radiation therapy and those made worse by such therapy. There was a low incidence of nausea and vomiting, as well as of severe bowel difficulty. Signs and symptoms of cystitis were present in almost all patients.

Fifteen patients had a contracted bladder as judged by the referring urologist.

Table V

COMPLICATIONS DURING THERAPY

Nausea	6
Hematuria	9
Dysuria	79
Frequency	94
Diarrhea	57
Rectal Bleeding	6
Other	14

However, 3 of these were known to exist before institution of radiation therapy, 3 occurred in conjunction with persistent disease, and 2 contracted bladders developed after infection following cystoscopy and biopsy 5 months after completion of radiation. These patients had been treated previously with multiple transurethral fulgurations and 4 had had segmental resections. The occurrence of contracted bladder according to stage is: Stage A—3/17, including the 2 cases following cystoscopy with infection, Stage B—4/75, Stage C—2/46, Stage D—1/54, an incidence of 5 per cent. Two additional patients had severe hemorrhagic cystitis which cleared on conservative management. Only 2 bowel complications requiring surgical intervention have occurred.

DISCUSSION

The patient population reported in this study is similar in age (median 66 years), sex distribution (ratio 3.2), presenting complaint (hematuria), and duration of disease to that in most reports from radiation therapy centers[4,5,8,10,11] and is slightly older than in surgical series. Like most radiation therapy series, the majority of patients were treated with irradiation after failure of one or more definitive surgical procedures. The improvement in survival to be expected in a group of patients treated primarily with radiation therapy is not yet known, although no difference from secondarily treated patients has been found in one nonrandomized study.[9]

Because of the abnormal chemical composition of the urine bathing the mucosa in many patients with bladder cancer and the multiple sites of involvement found especially in Stages A and B, we believe that the minimum treatment volume should be the entire bladder. Furthermore, Baker, Govan and Sawyer[1] demonstrated extensive circumferential spread of dye through the bladder wall following injection of 0.1 ml. of an India ink suspension into a single site.

The high incidence of lymph node involvement in tumors invading muscle and perivesical tissues makes *en bloc* treatment of the entire pelvis the most logical approach once invasion has been demonstrated. The improvement in survival in Stages B and C over patients treated surgically may be due to the adequacy of irradiation of the pelvic lymph nodes.

We are able to confirm a previous impression that death from disease usually occurs within 3 years in those patients who are not cured. Figure 4, *a–c* shows the cumulative death curves in Stages B, C, and D. All deaths occurred within 33 months in Stages C and D. Ninety per cent of deaths occurred at 11 months in Stage D, 21 months in Stage C and 30 months in Stage B. In addition, the incidence of proven metastatic disease at the time of death was greatest in those patients originally classified as Stage D or C and less in those staged as B. The major causes of death have been secondary to local pelvic tumor.

We have demonstrated that it is possible to treat the bladder and regional lymph nodes to 6,000 rads in 6 to 8 weeks with a relatively low incidence of complications. It is possible that the incidence of complications may be decreased by (1) sterilizing the urine before instituting therapy, (2) waiting for healing after surgery before commencing radiation therapy, and (3) delaying follow-up cystoscopy until full recovery from radiation reaction.

CONCLUSIONS

1. A significant number of patients with carcinoma of the urinary bladder may be cured with modern supervoltage roentgen therapy.

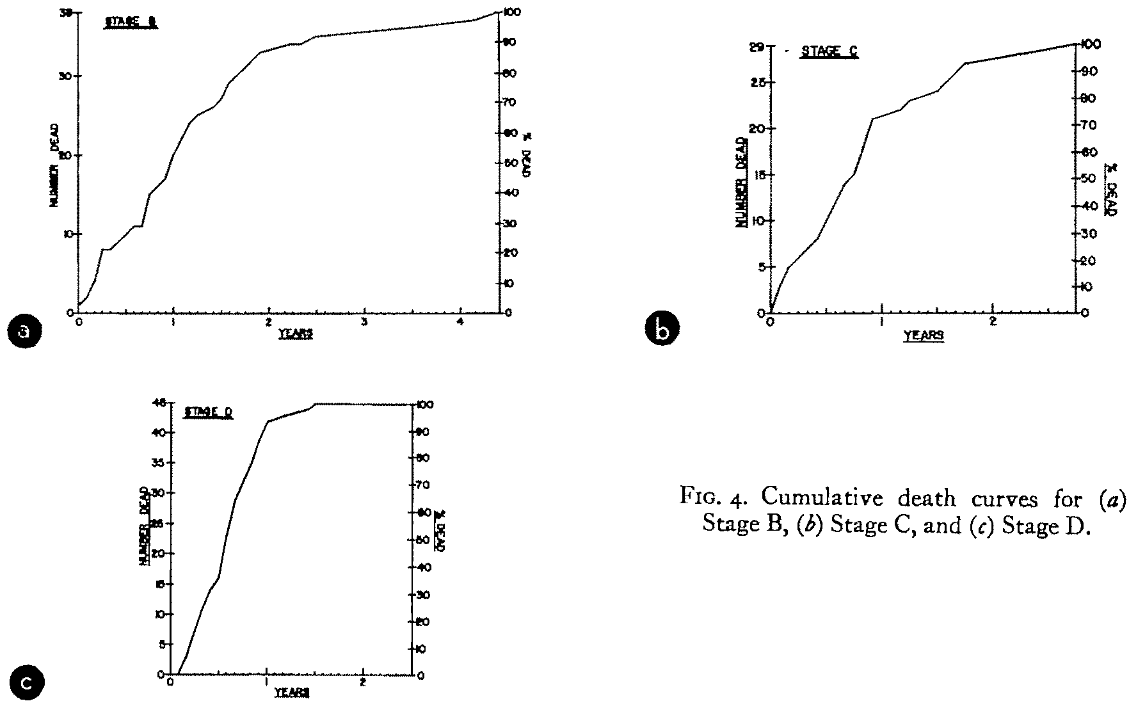

Fig. 4. Cumulative death curves for (*a*) Stage B, (*b*) Stage C, and (*c*) Stage D.

2. It is possible for the entire pelvis to absorb 6,000 rads and the bladder an additional 1,000 rads with a low incidence of complications.

3. Berkson-Gage[2] survival rates at 5 years are 32 per cent in Stage B and 25 per cent in Stage C.

4. An occasional patient with Stage D disease may be cured by adequate radiation therapy.

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SQUAMOUS CELL PAPILLOMATOSIS OF THE MALE URETHRA*

CO^{60} TUBE TANDEM TREATMENT

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BENIGN tumors of the urethra are rare. They can be divided into two groups; namely, those of epithelial origin and those arising from the connective tissue base of the urethral wall. The most common benign tumors of the male urethra are cysts, polyps, papillomas, adenomas and angiomas. Papillomas, while they may arise at any point along the urethral tract, are most commonly found about the vesical neck at, or near, the meatus. They rarely occur singly and resemble condylomas of the glans penis.

Vernon and Wilkins[14] point out that urethral papillomas may arise as a seedling growth from a vesical papilloma. This genesis has been especially noted since the introduction of the cystoscope. They suggest instilling a solution of 1:1,000 silver nitrate at the completion of cystoscopy to prevent such an occurrence.

Papillomas of the urethra occur in 1 per cent of boys undergoing urologic examinations. They usually arise from, or near, the verumontanum and are considered rare. In 1,770 examinations in children, Kjellberg[5] found only one polyp. Stephens[12] considered them to be of congenital origin. Multiple and extensive growths are occasionally seen. They may cause complete obstruction of the urethra with tremendous dilatation behind a mass of polyps. Papillomatous growth might cover the entire urethra.[11]

The mucous membrane of the normal male urethra is composed of transitional cells in the prostatic portion, columnar cells in the bulbo-membranous part and squamous cells anteriorly. In order for papillomatous growths to be squamous cell in nature, they must have arisen either in cell rests, or more likely, by a process of metaplasia due to infection and irritation. According to Kretschmer,[4] development of squamous cell papilloma involving the entire urethra could be explained on the basis of squamous cell metaplasia with a formation of patches of squamous cell condylomas.

A history of chronic urethritis practically always accompanies papillomas of the urethra. This may be due to gonorrhea or may be nonspecific. Other conditions most commonly preceding papillomas are stricture of the urethra, trauma or irritation of a chemical nature. According to Scholl and Braasch,[11] papillomas are often seen as a result of urethral infection. They occur mainly in the region of the verumontanum and the internal sphincter.

Graves and Guiss[3] report only 1 case of carcinoma of the male urethra in 19,000 admissions over a period of 14 years at Pondville State Hospital. During the same period of time, 10 cases of carcinoma of the female urethra were recorded at the same hospital. Kretschmer[4] reported a case of papillary carcinoma of the urethra in which many small papillary tumors were removed by curettage 25 years previously. Many papillomas, however, were discovered following amputation of the penis. It is a question of conjecture whether or not papillomas precede the development of carcinoma, or only present the predisposing factor.

Symptoms, according to Morrow *et al.*,[8] are as follows: burning and frequency, hematuria, urethral bleeding, growth in the urethra, urethral discharge, change in the character of stream, fistula formation and dyspareunia.

Diagnosis is established by urethroscopic examination, biopsy and urethrography. For a relatively small growth in the region of the fossa navicularis, radium is the choice of treatment for destroying the tumor. Fulguration is recommended to destroy small lesions in the anterior urethra. Lindner and Pasquier[5] reported a case of condylomas involving the entire urethra from the bladder neck to the external meatus. The lesions were treated by subtotal amputation of the penis and transurethral fulguration of the condylomas of the remaining portion. There are very few reports of similar cases in the literature. According to Graves and Guiss,[3] electrocauterization and chemical destruction are followed by stubborn recurrences. Morrow *et al.*[8] state that in 2 cases of papillomas involving the urethra radium therapy was employed with apparently good results. Van Herik,[13] referring to Morrow and co-workers' 2 cases treated at the Mayo Clinic, states that one of them was diagnosed as papilloma of the urethra and was treated by means of fulguration followed by radium therapy within the urethra. Radon was employed in a dose of 62 mc in a tube of 1 cm. active length filtered by the equivalent of 1.5 mm. of platinum and covered by rubber tubing 1 mm. thick. This tube was left in place within the urethra, at the level of the fulgurated area, for 1 hour to deliver 62 mc hours. The patient never returned to the Mayo Clinic for follow-up studies. The second case, treated by radium, was very similar to the first one, except that the papilloma was excised without fulguration and was then treated with intraurethral radium to the extent of 50 mg. hours. This patient was apparently treated with good result because he showed no evidence of recurrence in follow-up examinations. Murphy[9] reported a case of a 30 year old patient with multiple transitional cell papillomas involving the entire urethra. He treated the patient by using deep roentgen-ray therapy (250 kv. peak, half value layer 2.5 mm. Cu, field size 12×3 cm.). The total surface dose delivered in 19 equal treatments (25 treatment days) over the entire penis was 3,800 r (3,648 rads). The 3 cm. depth dose was 2,830 r (2,717 rads). One month after irradiation, only a small residual tumor remained. The skin reaction was intense, but recovery was complete within 1 month. The patient is still being followed. The latest information was that 2 small papillomas were found and were benign.[10]

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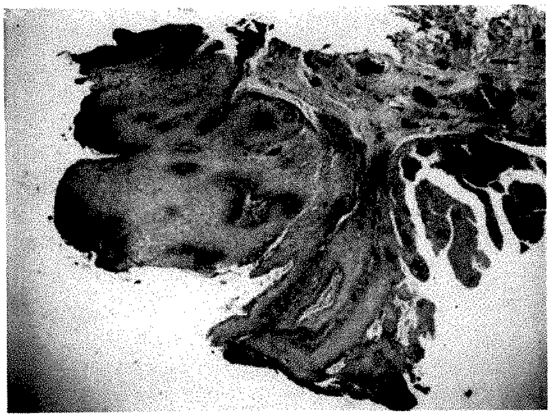

Fig. 1. Photomicrograph shows general pattern of epithelium.

Prognosis is more favorable in anterior lesions than in posterior ones. This fact may be due to delayed diagnosis in posterior lesions. Because of the tendency to recurrence, the patient should be followed every 3 to 6 months for 2 to 3 years. Sufficient data are not available at the present time to evaluate roentgen-ray or radium therapy results.

REPORT OF A CASE

A 29 year old, Negro, married real estate dealer appeared at the Out-Patient Clinics of Cleveland Metropolitan General Hospital in April, 1962, after having been treated twice at another hospital in the past year, for condylomas of the glans penis. Treatment consisted of circumcision and fulguration of the tumors. His present complaint was difficulty in voiding, due to a small tumor protruding from the urethral meatus. Cystoscopy showed multiple papillomas involving the entire urethra. Several papillomas were excised near the meatus for the purpose of histologic diagnosis. Biopsy specimen showed squamous cell papilloma (Fig. 1 and 2). A urethrogram (Fig. 3) made after the biopsy revealed multiple small rounded filling defects varying in size from 2 to 3 mm. in diameter. In view of the extensive involvement of the urethra and the age of the patient, the treatment of choice was cobalt 60 tube tandem

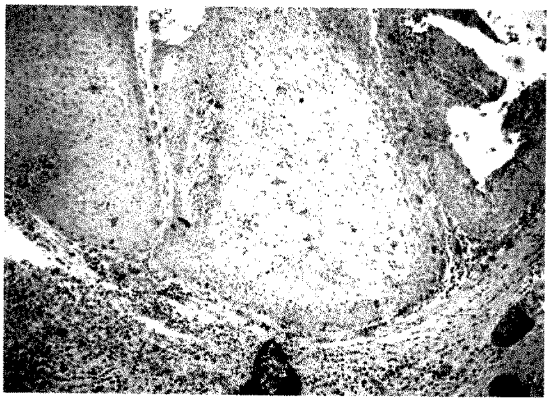

FIG. 2. Photomicrograph shows cellular detail. The specimen is composed of central coarse, fibrovascular tissue lined by squamous epithelium forming in places delicate papillary fronds. There is keratinization of individual cells and occasional clumps of polymorphonuclear leukocytes are present within the squamous epithelium. Basement membranes are intact. The underlying urethral stroma contains lymphocytes and occasional polymorphonuclear leukocytes. In some areas, uninvolved transitional cell epithelium is identified.

application rather than an extensive surgical procedure. To avoid stricture of the urethra, the dose was planned over a longer period of time. The plan was to deliver about 6,000 gamma r to the anterior urethra, and about 4,000 r to the posterior urethral mucosa, in 10 treatments in an over-all time of about 1 month. A split-course technique was chosen using two different cobalt 60 tandems and delivering a precalculated dose in two courses.

Tandem I: No. 14 Fr. soft rubber catheter was used loaded with 5 cobalt 60 tubes (Fig. 4), which were of 2 cm. total length, 1.6 cm. active length, 6.5 mg./cm. linear activity, each containing 9.74 mg. of radium equivalent. The total length of the tandem was 10 cm., the active length 9.5 cm. and the diameter 0.5 cm.

The patient was treated on April 12, 1962 and April 13, 1962, each treatment lasting 1½ hours, or a total of 3 hours. The calculated dose delivered in 1 hour to the urethral mucosa was 497.2 gamma r. The dose delivered to the anterior urethra in 3 hours was 1,491.6 gamma r.

Tandem II: No. 14 Fr. soft rubber catheter was used, loaded with 9 tubes (Fig. 5) of the same length as Tandem I. The total length of the tandem was 18 cm., the active length 17.5 cm. and the diameter 0.5 cm. The dose delivered in 1 hour to the urethral mucosa was 488.6 gamma r.

With this tandem, the patient was treated four times on 4 consecutive days (April 18, 1962 to April 22, 1962), 2 days following treatment with the first tandem. The total treatment time was 5½ hours. The dose delivered to the anterior urethra and part of the posterior urethra, up to about 4–5 cm. from the trigone of the bladder, was 2,687.3 gamma r.

The total treatment time of the first course using both Tandems I and II was 8½ hours; the total treatment days were 8. The dose delivered to the anterior urethra was 4,178.9 gamma r and to the posterior urethra 2,687.3 gamma r. The dose delivered to the posterior urethra was purposely smaller because of the possibility of edema of the bladder neck and also of stricture and adhesions at a later date in the regions of the external sphincter and verumontanum. Both catheters containing cobalt 60 tandems were introduced into the urethra to the marked

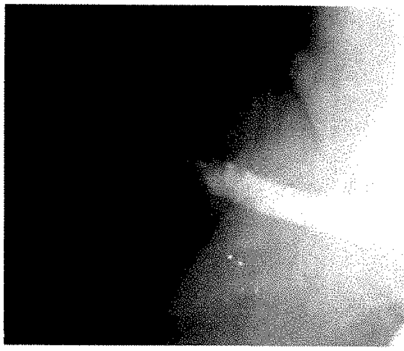

FIG. 3. Urethrogram before treatment shows multiple small, round filling defects.

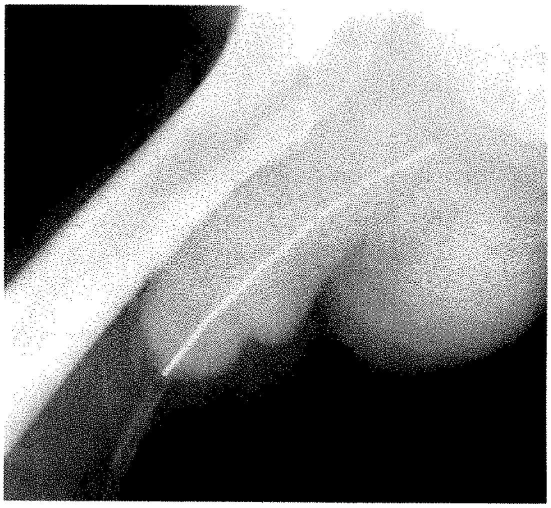

FIG. 4. Urethrogram shows 5 cobalt 60 tube tandem in the anterior urethra.

line using 2 per cent xylocaine ointment as a lubricant and anesthetic. The patient tolerated the procedure well with minimal discomfort and the only symptom was frequency after 10 days following treatment. For 2 weeks following treatment, the urethra was dilated every other day with No. 14–No. 16 Fr. catheters and then No. 18 Fr. catheters, using 1 per cent prednisone cream (Medrol) as a lubricant in order to prevent postradiation adhesions and to diminish radiation mucositis. The full dose of radiation was not delivered in 1 month as planned because 6 weeks following irradiation two residual papillomas were found in the prostatic urethra and two in the region of the external sphincter. These papillomas were fulgurated during cystoscopy. About 2 months following fulguration, a few persistent residual papillomas were found in the anterior urethra. A second course of irradiation using cobalt 60 Tandem 1 was instituted. The patient was treated again on June 12, 1962 and June 13, 1962. An additional 1,960 gamma r were delivered to the anterior urethra in two treatments of 2 hours each. The total dose delivered to the urethral mucosa, in two courses of treatment in an over-all time of 2 months, was 6,138 gamma r to the anterior urethra and 2,687.3 gamma r to the posterior urethra. A urethrogram made 1 month later demonstrated an almost normal urethra (Fig. 6). The dose delivered to both testicles through the entire course of treatment was negligible and would not produce sterility, although it might produce some lethal genes.

DISCUSSION

There is no known method of accurately measuring the dose of radiation at the distances involved. The patient was treated with a cobalt 60 tandem and the surface dose at the urethral mucosa was calculated using the Quimby,[2] and Paterson and Parker[7] tables for linear radium sources. The exact calculation of the dose rate at the urethral mucosa, opposite the center of the cobalt 60 tubes and at the point of contact of the tubes, is difficult as it is a function of variables. These variables are treatment distance, backscatter, self-absorption of cobalt 60 sources, type of absorber used as a filter and length of applicator.

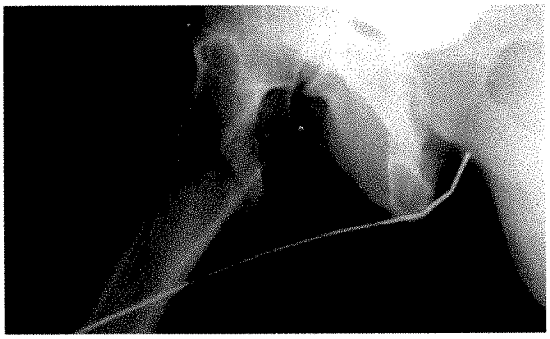

FIG. 5. Urethrogram shows 9 cobalt 60 tube tandem in the anterior, middle, and part of the posterior urethra.

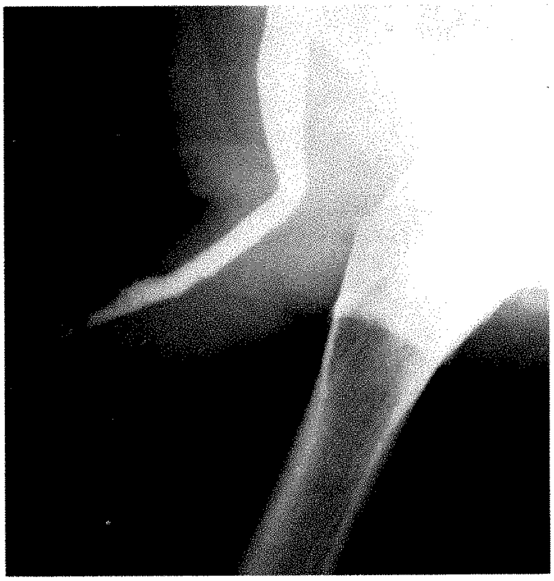

FIG. 6. Urethrogram taken 1 month following treatments shows disappearance of the papillomas and presence of irregularity in the fossa navicularis due to fibrosis following previous surgery.

For short treatment distance when using an applicator of long active length, the inverse square law does not apply. The method accepted in our case is not too exact, and gives an idea of the dose delivered at the center of the tandem. The dose opposite the point of contact of the tubes might be half that opposite the center of the tube.

Both Quimby, and Paterson and Parker charts are calculated for 0.5 mm. or 1 mm. Pt filter. In our case, the filter is 0.3 mm. of steel. Although it is sufficient to remove weak radiation produced by cobalt 60, in view of the lower density of steel as compared to Pt (Fe = 7.90 gm./cm.^{3}, and Pt

$=21.27$ gm./cm.^{3}) and the lower linear absorption coefficient of steel (Fe$=0.0129/0.3$ mm., and Pt$=0.0695/0.5$ mm.), the biologic effect of cobalt 60 at the near proximity of the tube should be greater. The dose at close range delivered by cobalt 60 tubes is appreciably greater than for radium tubes of the same nominal strength. The dose ratio of cobalt 60 to radium at the surface of the tube is 1.75/1 and at 0.25 cm. distance is 1.15/1.[1]

Self-absorption of cobalt 60 is of great importance and the influence it has on the dose delivered could be calculated by using Sievert's integrals. In view of the tremendous amount of calculation involved, the problem could be solved by using an electronic computer.

The type of absorber used for construction of cobalt 60 tandem absorption in 1.7 mm. of rubber was considered. It should be negligible as the absorption coefficient for rubber is very similar to that of muscle. (The absorption coefficient for thickness of 1 mm. of rubber is 0.0023 and for the same thickness of muscle is 0.0024.)

Both tandems are unusually long considering the treatment distance. The maximum dose would be delivered opposite the center of the tandem with the increased theoretic possibility of producing stricture and adhesions in the urethra. This probably could be avoided by using a slightly weaker source at the center of the tandem. From this point of view, the tandem arranged with multiple radiation sources is better than one single source of radiation.

SUMMARY

A case of squamous cell papillomatosis involving the entire male urethra is presented. The patient was treated using two cobalt 60 tandems. The dose on the urethral mucosa was calculated by using Quimby, and Paterson and Parker tables for linear sources. Peculiar problems related to the very short treatment distance, very long active length of the source, self-absorption of cobalt 60 and backscatter are discussed. If a 15 per cent greater dose of cobalt 60 tubes as compared to radium sources is accepted at 0.25 cm. treatment distance, the difference between the dose calculated for treatment and computed is negligible (see article that follows).

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SQUAMOUS CELL PAPILLOMATOSIS OF THE MALE URETHRA

WALL-ABSORPTION, SELF-ABSORPTION AND DEPTH DOSE EFFECTS IN A TANDEM ARRANGEMENT OF CO^{60} NEEDLES

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As NOTED in the preceding paper, a case of squamous cell papillomatosis involving the entire length of the urethra was treated successfully through the use of two tandem arrangements of Co^{60} needles. In view of the fact that examples of this disease are rare and little is known about the optimum dosage that should be delivered, the approximate dosage was originally estimated on the basis of the Quimby, and Paterson and Parker tables for linear radium sources in a 0.5 mm. Pt tube. Since then, however, the question arose as to the exact dose the patient received and the following is the result of such deliberation.

One tandem was loaded with 9 identical needles in contact end on end and the other with 5 identical needles in a similar arrangement. In both a rubber tube of 1.7 mm. wall thickness was used to contain the needles. Since the epithelial layer and the mucosa are located in a very thin layer on the inside surface of the urethra and since the tandems stretched the tissue so that this layer was at the outer surface of the rubber, it was felt desirable to calculate the dosage on a line 0.25 cm. from and parallel to the axis of the tandems. At this small distance, it is obvious that the dosage will change from a minimum in the plane perpendicular to the point of contact between the needles to a maximum in the plane perpendicular to the center of each needle. Furthermore, self-absorbtion, wall-absorbtion, and build-up due to gamma ray diffusion and electron scattering in an extended medium should all be of some importance.

Each needle was a steel tube of 1.6 mm. diameter, 20 mm. total length, 16 mm. inside length and a wall thickness 0.25 mm. containing two activated cobalt wires. One wire was 0.45 mm. in diameter by 16 mm. long and the other 0.67 mm. in diameter by 14.5 mm. long. At the time of treatment, each needle contained 9.74 mg. radium equivalent.

While some of the calculations will show certain factors to be of little importance, this could not be foreseen and are included here to demonstrate the insensitivity of the actual dosage to such factors at these small distances. Actually, many papers—primarily experimental—have been published on the dosage close to both radium and cobalt needles.[1] However, the results have neither been accurate enough or general enough for the purposes desired here.

In all of the following calculations it will be assumed that the steel walls and rubber tube are adequate to stop all beta particles (for Co^{60} 0.308 mev. betas the maximum range is 80 mg./cm.^{2} of Al) and that the build-up in the walls due to Compton absorption is negligible.

Firstly, let us consider a line source in air of specific activity q' mc/cm. of Co^{60} as shown in Figure 1 (disregarding the absorbing wall). The intensity at P may easily be shown to be

$$I_p = \frac{\Gamma q'}{a} \int_{\theta_1}^{\theta_2} d\theta = \frac{\Gamma q'}{a} (\theta_2 - \theta_1), \qquad (1)$$

where Γ is the dose-rate constant. If a tubing wall the thickness of t is added as shown in Figure 1, the equation (1) is changed to

$$I_p = \frac{\Gamma q'}{a} \int_{\theta_1}^{\theta_2} e^{-\mu t/\cos\theta} d\theta, \qquad (2)$$

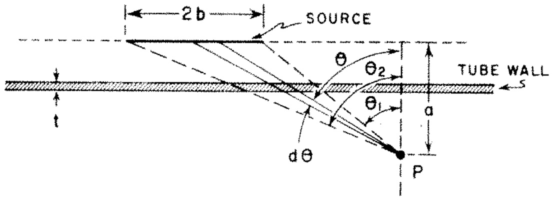


Fig. 1. Assumed geometry for an ideal linear source of finite length contained in a tube of infinite length.

which is the well known Sievert integral. Equation (2) holds for a finite length source in an infinitely long tube which is a very close approximation to our case where the needles are butted on end. Since the two wires in each needle are close packed with the average moment on the axis of the needle, it is reasonable to substitute one wire for the two with a volume equal to the sum of the two individual wires. In this case one wire of 0.8 mm. diameter by 16 mm. length may be used. Also, symmetry considerations demand that this one wire with activity distributed in volume be equivalent to an infinitesimal line source immersed in a solid tube of inactive cobalt metal. The only question is that of the wall thickness of this cobalt tube. If we look at any line from P through this active wire, we see that it consists of a series of point sources over a length $2b$, a distance a away from P, as shown in Figure 2. If the cobalt has a linear absorption coefficient μ for its own radiation, we may write for intensity at P

$$I = \Gamma q \int_{a-b}^{a+b} \frac{e^{-\mu(x-a+b)}}{x^2}\, dx. \qquad (3)$$

Integrating and neglecting higher powers of μx we obtain

$$I = \frac{2qb\Gamma}{a^2}\, e^{-\mu b}, \qquad (4)$$

which is the same expression one would obtain for all the point sources (total strength $2qb$) concentrated at distance a with an absorber b units thick between this point source and point P. The same can be shown to be true of an array of line sources.

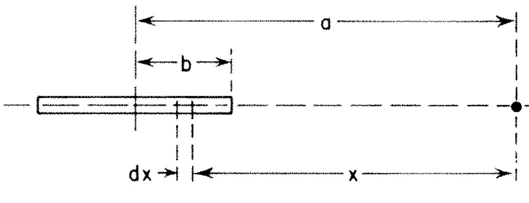


Fig. 2. Assumed geometry for a linear array of point sources also capable of absorbing radiation.

Since our objective is to obtain a calculable model within a given accuracy, it is obvious that to reinsert the effect of self-absorption in our final picture, we must first determine the magnitude of its effect on the original source strength. This will be admittedly small but will serve to illustrate the over-all picture. The calibration procedure of these needles was done at distances large compared with the size of the needle so that we may consider the source to be a point source surrounded by a 0.4 mm. cobalt shield. This will effectively reduce the intensity by $e^{-\mu t} = 0.982$, a rather negligible effect. Since each source was found to be 9.74 mg. radium equivalent and the most reliable conversion factor is 0.630, we find the source strength to be

$$\mathcal{Q} = \left(\frac{9.74}{0.982}\right)(0.630) = 6.24 \text{ mc Co}^{60}.$$

The last factor to be considered is the "depth-dose" effect or effect of electron build-up in the medium. The linear absorption coefficient in water is 0.0632 cm.$^{-1}$ for Co^{60} radiation. Figure 3 shows that if we now examine the intensity distribution in

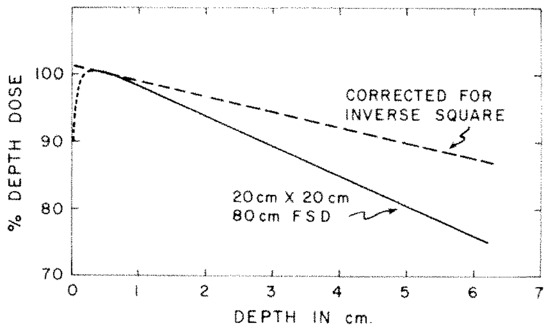


Fig. 3. Depth dose data for Co^{60} radiation an infinite distance away from the absorbing medium.

an extended medium for a plane parallel beam we see that it rises to a maximum at about 2.5 mm. and then falls as $e^{-\mu x}$, where $\mu = 0.023$ cm.$^{-1}$. This, of course, is due to build-up. These data were obtained from those given by Johns[3] for a 20 cm.×20 cm. field at 80 cm. focus skin distance and then subtracting the inverse square effect. To a very good approximation, then, we can assume our needle to be a truly linear source immersed in a cobalt tube of absorption μc and thickness tc in turn surrounded by a steel tube of thickness ts and absorption μs and finally, both tubes surrounded by a water tube of thickness $(a\text{-}tc\text{-}ts)$ and absorption 0.023 cm.$^{-1}$ This gives then for our final Sievert integral:

$$I = \frac{\Gamma q'}{a}\int_{\theta_1}^{\theta_2} \exp\left\{-\left[\frac{\mu ctc + \mu sts + 0.023(a - tc - ts)}{\cos\theta}\right]\right\} d\theta. \tag{5}$$

$$I = \frac{\Gamma q'}{0.25}\int_{\theta_1}^{\theta_2} \exp\left\{-\left[\frac{0.0176 + 0.010 + 0.0058}{\cos\theta}\right]\right\} d\theta,$$

$$I = 4\Gamma q'\int_{\theta_1}^{\theta_2} \exp\left[-\frac{0.0334}{\cos\theta}\right] d\theta. \tag{6}$$

It is interesting that the self-absorption in the cobalt is the most predominant factor and the depth dose the least important. While the above integral can be evaluated numerically, it was actually programmed and solved on a GE 225 computer at the Western Reserve University Computing Center. The results of this calculation for the intensity on a line 2.5 mm. from and parallel to the axis of a 2 cm. Co^{60} needle are shown in Table I. Column (3) is the ratio of equation (6) to equation (1) at the same point which in essence is the correction required for an unencapsulated line source. While this correction is only 5 per cent at the center, it becomes greater at the larger distances as might be expected. At these distances, however, the intensity is so low as to make such corrections relatively unimportant. Should a real single needle be used with a finite tube enclosure and end wall, these results would have to be modified (increased) at distances greater than about 40 to 50 mm. Table II is a listing of the intensities in a plane perpendicular to the axis and passing through the center of the needle.

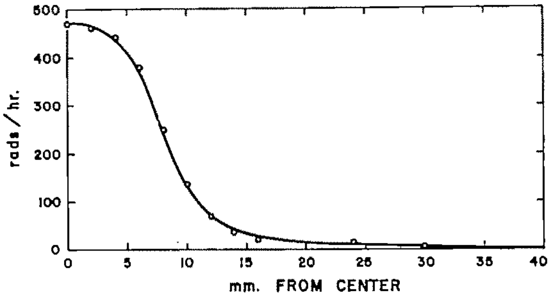


FIG. 4. Intensity at a distance 2.5 mm. away from and parallel to the axis of a linear source with all effects included as described. The circles are experimental check points.

Again, for large distances where, as in this case, water absorption becomes dominant, the correction for an ideal line source is larger but the intensities are so low as to be insignificant. No correction for end caps would be required here if a real single needle were used. Regarding the value of $\Gamma q'$, we have $q' = 3.81$ mc/cm., $\Gamma = 13.1$ r–cm.^{2}/mc–hr., and a conversion factor of 0.965 rads/r for muscle such that $\Gamma q' = 48.3$ rads–cm./hr. The data of Table I are plotted as the smooth line in Figure 4. The circles are the results of a film densitometric determination of the intensity distribution in a plane 2.5 mm. form a single Co^{60} needle. The whole needle was immersed in lucite with a sheet of film located 2.5 mm. from the center and parallel to the axis of the needle. After an hour of exposure and the usual developing precautions, density determinations were made and, in turn, were converted to intensity by a predetermined calibration curve. The check is

Table I

INTENSITY ALONG A LINE 2.5 MM. FROM AND PARALLEL TO THE AXIS OF A 2 CM. CO^{60} NEEDLE WITH AN INFINITE LENGTH WALL

Distance from Center (mm.)	Intensity (rads/hr.)	Ideal Line Source Correction
0	470.5	0.945
2	463.3	
4	436.4	0.930
6	368.1	
8	236.5	0.844
10	124.2	0.830
12	69.9	
14	44.3	0.803
16	30.5	
18	22.2	0.750
20	16.9	
22	13.2	
24	10.6	0.675
26	8.63	
28	7.14	
30	5.99	0.605
32	5.07	
34	4.34	
36	3.74	
38	3.25	
40	2.84	

Table II

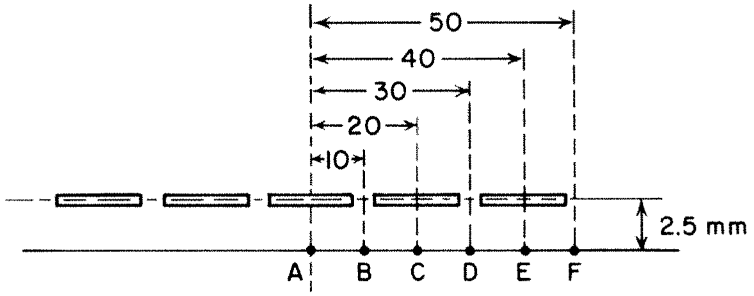
INTENSITY IN A PLANE PERPENDICULAR TO THE AXIS AND PASSING THROUGH THE CENTER OF A 2 CM. CO^{60} NEEDLE

Radial Distance from Center (cm.)	Intensity (rads/hr.)	Ideal Line Source Correction
0.25	470.5	0.95
0.50	186.7	0.95
0.75	102.6	0.95
1.0	62.0	0.95
2.0	17.2	0.93
3.0	7.8	0.92
4.0	4.1	0.89
5.0	2.7	0.87

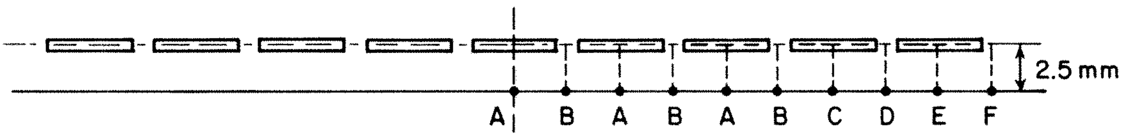
Table III

INTENSITIES AT POINTS INDICATED IN FIGURE 5

Points	Rads/hr.
A	510
B	262
C	507
D	256
E	490
F	132



(a) FIVE NEEDLES



(b) NINE NEEDLES

Fig. 5. Geometric arrangement of the (*a*) 5 and (*b*) 9 needle tandems.

exceptionally remarkable considering the difficulty of locating the exact center of the needle and the use of a 1 mm. diameter light beam in the densitometer. Actually, the accuracy of the experimental determination is not as good as indicated and more faith should be placed in the theoretic calculation than the experiment.

To determine the intensity distribution at 2.5 mm. from the tandems used in this treatment, one merely has to superpose the data in Table I for the proper number of needles suitably displaced from each other as shown in Figure 5. The intensities for the maxima and minima of a 5 needle tandem are shown in Table III and the complete distribution is shown in Figure 6. These additions were also programmed, and performed quite easily and quickly by the computer.

It is to be noticed that the intensity varies as much as 2:1 at these short distances which, like grid therapy, may prove to be of aid in the recovery of the normal tissue after treatment.

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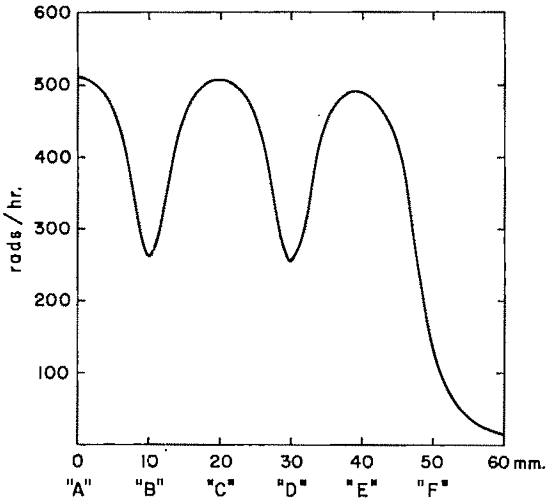

FIG. 6. Intensity on a line 2.5 mm. away from and parallel to the axis of a 5 needle tandem.

The author is indebted to Mr. E. Chernak for his assistance with the densitometric determinations of dosage and to Dr. A. S. Littel for his assistance in programming the computer for the results presented here.

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GERMINAL CELL TUMORS OF THE TESTIS*

A REPORT OF 102 CASES

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THIS study consists of 102 cases of germinal cell tumors of the testis treated at the Atlanta Veterans Administration Hospital from 1935 to 1957. Fifty-seven of these patients are now deceased and 45 are living and have been followed 5 or more years. Microscopic sections were available for review in 86 of the 102 cases and the material was classified after the method of Dixon and Moore.[5] In 1958, 30 of the 45 living patients were recalled for detailed study.

While the ages of the patients ranged from 21 to 67 years, their median age was 30 years. Figure 1 shows that the highest incidence was in the 20 to 29 year old group.

Cryptorchism occurs in less than 1 to 2 per cent of the male population; however, 1 of every 10 patients with carcinoma of the testis has a history of undescended testicle.[7] A similar incidence was found in our group. Although 10 patients gave a history of malposition of the testicle at some time during their lives, only 1 patient presented with malposition of the testicle at the time of surgery.

Only 1 patient had tumors affecting both testes.

Two Negro patients were seen.

DIAGNOSIS: SIGNS AND SYMPTOMS

Duration of symptoms prior to surgery varied from 1 day to 7 years. An average duration of symptoms of 10 months was found in both the living and deceased groups. Ninety-four patients noted testicular enlargement prior to admission, but only 51 complained of pain. In the deceased group 58 per cent as contrasted with 42 per cent of the surviving group noted pain. Previous authors have pointed out the poor prognosis of patients presenting with pain.[1]

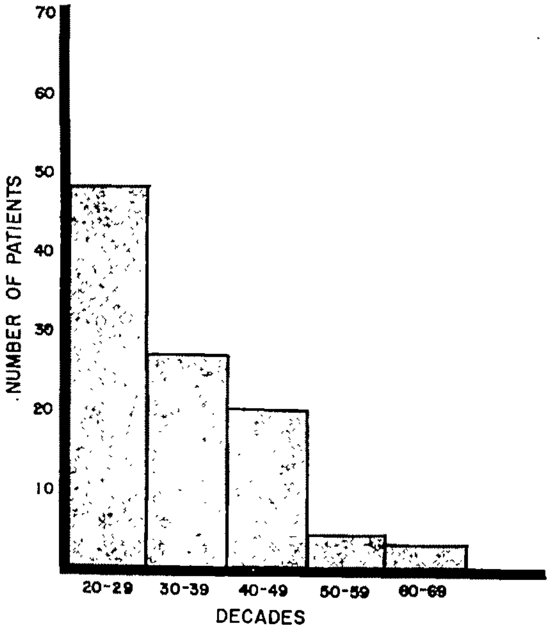

FIG. 1. Age at time of diagnosis.

Gynecomastia was described in 10 patients. Since 9 of the 10 were in the deceased group, this sign appeared to indicate a poor prognosis. Histologically, gynecomastia was associated with an element of embryonal origin or choriocarcinoma.

Many patients gave a history of treatment for an inflammatory condition of the testes prior to admission. In 9 patients a temperature above 100° F. was recorded on admission.

Involvement of the testis occurred on the right side in 56 patients and on the left side in 46 patients.

ENDOCRINE ASPECTS

Prolan A (gonadotropins) determinations were performed in the early years covered

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* From the Veterans Administration Hospital, Atlanta, Georgia, and Emory University School of Medicine.

TABLE I

ENDOCRINE DETERMINATIONS

Gonadotropins	Deceased Patients	Living Patients
Initial Prolan A Determinations	Normal	<50
0–50 mouse units	8	11
51–200 mouse units	7	5
>200 mouse units	15	10
A–Z test	2+ and 1−	0+ and 0−
Friedman test	4+ and 4−	0+ and 7−
Follow-up Gonadotropins on Living Patients	Normal	<52.8
0–52.8 mouse units		18
$>52.8<211$ mouse units		5
>211 mouse units		1
17 Ketosteroids normal 8–22 mg./24 hr.		
Follow-up Patients		
0–8 mg./24 hr.		5
8–22 mg./24 hr.		20

by this study by the Veterans Administration reference laboratory at Hines, Illinois. These assays are believed to be based on the techniques described by Cutler an Owen.[4] Later, gonadotropin assays were performed by a slightly different method at Atlanta Veterans Administration Hospital.[2]

The initial gonadotropins in most instances were collected after surgery. In only a few patients were serial gonadotropin titers performed. It can be seen from Table I that elevated initial titers did not necessarily indicate a poor prognosis. The highest recorded initial titer of 3,300 mouse units was in a patient who survived. Where serial titers were obtained, a rising titer was more often associated with a poor prognosis and implied active metastatic disease. Conversely, a falling titer was more often associated with a better prognosis.

On follow-up examination of surviving patients in 1958, only 1 of 24 had a titer of greater than 211 mouse units. This patient had atrophy of the remaining testicle and this titer probably represented a castration effect.

Aschheim-Zondek and Friedman tests were performed in some patients postoperatively. Two out of 3 Aschheim-Zondek tests[1] done in the deceased group were positive. Four out of 8 Friedman tests[6] were positive in the deceased group and 7 Friedman tests were negative in the living group.

Frog tests[8] were performed on freshly voided urine samples on 30 follow-up patients. Twenty-eight tests were negative. Two false positive tests were encountered. These had normal gonadotropin titers when measured by mouse units.

Seventeen ketosteroid determinations[9] were performed on 25 living follow-up patients with 20 having normal titers and 5 having minimally decreased titers. The low titers may be explained in part by advancing years. None of the 17 ketosteroids were below 6 mg./24 hours.

Seventeen hydroxysteroid determinations[3] were performed on 25 living follow-up patients. Twenty were normal and 4 showed slight increase, but probably represented normal titers.

Thus the 17 ketosteroids and 17 hydroxysteroids did not indicate any adrenal hypofunction which might have been a complication of radiation therapy.

PATHOLOGY

The tumors in this series were re-examined and classified according to the histo-

TABLE II

DISTRIBUTION OF METASTATIC LESIONS FOUND AT AUTOPSY

Patient	Pathologic Diagnosis	Lungs and Pleura	Lymph Nodes			Liver	Kidneys	Adrenals	Spleen	Peritoneum	Pancreas	Brain	Cranial Vault	Thoracic Wall	Colon	Pituitary	Diaphragm	Aorta	Vertebrae	Pericardium	Gynecomastia
			Thoracic	Abdominal	Inguinal																
S.M.	Seminoma	+	+	+		+	+	+	+	+		+	+			+					
H.M.	Embryonal and Choriocarcinoma	+	+	+	+	+	+	+		+				+			+		+		+
M.P.	Embryonal Carcinoma	+	+	+	+		+														
H.B.	Embryonal Carcinoma	+	+	+			+		+			+								+	+
J.B.	Seminoma	+	+	+		+			+		+										
C.W.	Choriocarcinoma	+	+	+			+	+													+
H.K.	Embryonal Carcinoma	+	+										+	+							
J.H.	Seminoma	+				+			+	+											
J.L.	Embryonal Carcinoma	+	+			+		+													+
C.L.	Embryonal Carcinoma	+									+				+			+			
R.G.	Choriocarcinoma	+		+		+															+
L.B.	Embryonal Carcinoma	+		+																	
W.P.	Embryonal Carcinoma	+	+																		
A.W.*	Choriocarcinoma			+		+		+													

* Limited to abdomen.

logic criteria and nomenclature established by Dixon and Moore:[5]

(I) Seminoma, pure; (II) embryonal carcinoma, pure or with seminoma; (III) teratoma, pure or with seminoma; (IV) teratoma with either embryonal carcinoma or choriocarcinoma, or both, and with or without seminoma; and (V) choriocarcinoma, pure or with either seminoma or embryonal carcinoma or both. The available material consisted of one to several sections in 86 out of the 102 cases. In the remaining 16 cases, the description and diagnoses of the original examiner were re-interpreted according to the criteria of Dixon and Moore.[5]

Complete autopsy studies were available in 13 cases, and a study limited to the abdomen in 1. Table II gives the distribution of the metastatic lesions. The involvement indicates spread by both lymphatics and blood stream.

TREATMENT

Treatment of the testicular tumor was inguinal orchiectomy. No biopsy was taken because this destroys the tunica albuginea that tends to limit the disease. Following orchiectomy, the patient was given radiation therapy. The radiation given was quite variable. A number of patients had surgery and radiation prior to admission to this hospital. These were admitted for follow-up or treatment of further metastatic disease. Other patients were admitted in various stages of disease, with or without prior orchiectomy, for radiation therapy. Radiation therapy varied depending on the presence or absence of metastasis, the location and type of tumor, condition of the patient, and response.

The routine prophylactic irradiation was to lymphatic areas of the abdomen in all types of cases except choriocarcinoma. This treatment was delivered with orthovoltage equipment, 220 kv. Maximar with Thoreus filter, half value layer of 2.35 mm. Cu. Four to 5 portals, as shown in Figure 2, *A* and *B* covered the inguinal and abdominal areas up to the level of the epigastrium. Lower abdominal ports were outlined along the aorta corresponding to the side of the testicular involvement and extending only minimally across the midline. Upper abdominal ports were outlined to include the lymphatics of the renal pedicles, but were not so large that significant renal tissue was irradiated. Scrotal and inguinal ports were added when there was extension of the tumor through the tunica albuginea or when there was inguinal lymph node involvement. The mediastinum and left supraclavicular areas were not routinely irradiated. The tumor dosage at times was modified by

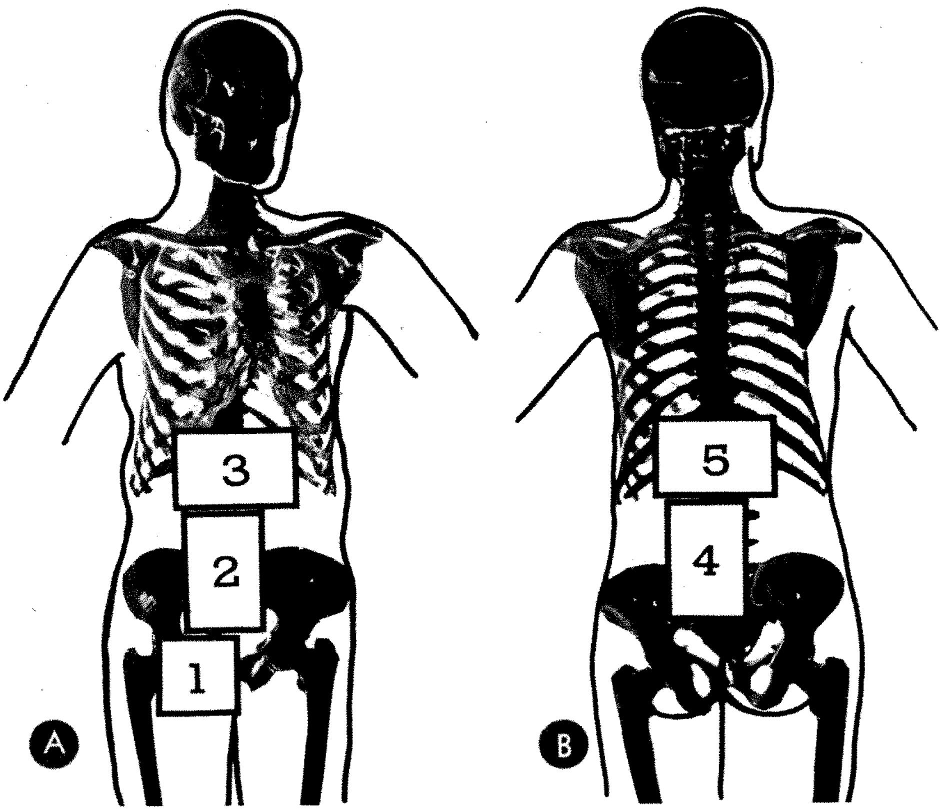

Fig. 2. (*A* and *B*) Diagrams showing areas of irradiation.

patient tolerance or leukopenia. Symptomatic irradiation was attempted by treatment of areas of involvement in patients with choriocarcinoma. A tumor dose of 1,600 r was attempted for seminoma and 2,500 to 3,500 r or higher for embryonal carcinoma or teratoma.

A number of patients had radiation treatment administered to other portals in the presence of metastatic disease. Some patients, treated elsewhere, received irradiation prophylactically to the mediastinum.

Because of the variability of technique, no attempt is made to evaluate any particular schedule of treatment; rather, the results are summarized.

RESULTS

In this series there was a 100 per cent follow-up. All living patients have been followed for at least 5 years and some for 15 years. Figure 3 shows the survival curves of patients with various types of tumor.

The 5 year survival rate for all patients was approximately 50 per cent (Fig. 4). However, no patients with choriocarcinoma survived after 26 months, all but 1 dying within the first year. Of 29 cases of pure seminoma, there was a 5 year survival rate of 80 per cent. Embryonal carcinoma and teratoma gave a prognosis between these two extremes.

Twenty-five patients who did not survive were seen prior to orchiectomy. Of these, 7 had metastatic disease in the chest on admission. Intravenous pyelography performed on 20 of these patients revealed deviation of the ureters in 8 patients.

COMPLICATIONS OF RADIATION THERAPY

Minor changes of the skin such as pigmentation and telangiectasia were noted.

In 1 patient severe damage was produced by irradiation given to a suprapubic

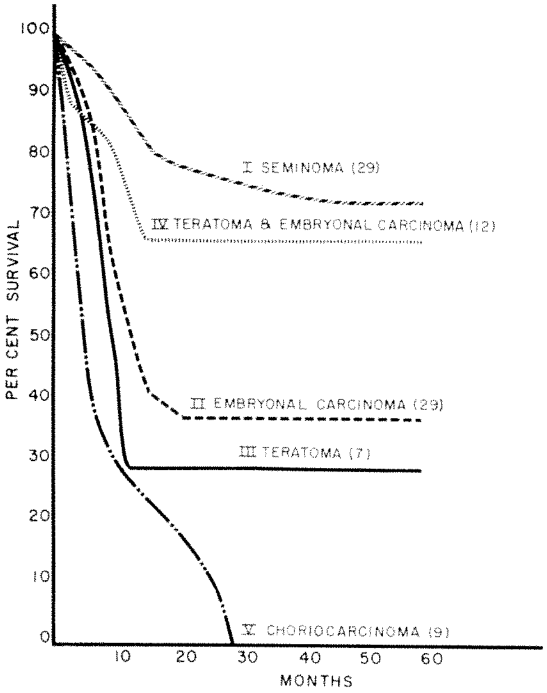

Fig. 3. Actual survival of germinal cell tumor of the testis cases according to group.

and corresponding posterior port. The treatment, in a patient 32 years of age, was given elsewhere in 1935, following a left orchiectomy for seminoma. This patient was first seen in this hospital in 1940, at which time there was ulceration of the suprapubic area. In addition, severe fibrosis and telangiectasia were noted of the skin in the posterior as well as the anterior port. The suprapubic lesion was removed elsewhere; this was reported as fibrosarcoma. In 1947 a right testicular tumor was removed; this was an embryonal carcinoma. Additional irradiation was given for metastatic disease of the right inguinal area. The most recent follow-up in July, 1963, revealed no malignant disease. The severe radiation damage of the back remains unchanged.

Radiation nephritis was seen in a 30 year old white male who had a testicular tumor removed in the Army in 1944. Blood pressure was 108/70 at that time. Three courses of radiation therapy were given. A pyelogram in August, 1944, was reported as showing normal renal size. The patient was admitted to this hospital in 1947 for treatment of severe hypertension. Pyelograms demonstrated bilateral small renal structures. The patient was alive in 1963 without evidence of malignant disease. The hypertension continues, but is controlled on medical management.

There were no instances of leukemia in this series of cases despite irradiation of large areas with high doses. One patient died of aplastic anemia. This patient had intensive abdominal irradiation for intra-abdominal metastatic disease.

BIOLOGIC EFFECTS OF RADIATION IN TESTICULAR TUMORS

Data were obtained about the progeny of 34 living married patients (Table III). Fifteen of these had received roentgen

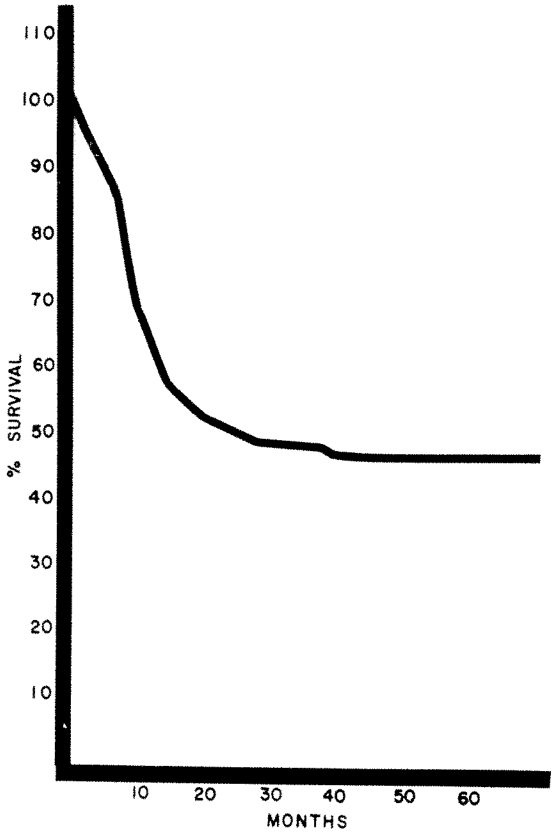

Fig. 4. Actual survival of all germinal cell tumor of the testis cases.

therapy to include the scrotal area; the remaining uninvolved testicle was, however, shielded with lead rubber, the equivalent of 2 mm. lead. Three of these 15 had normal children after their roentgen therapy. Nineteen patients had received roentgen therapy not including the scrotal area. Of these, 6 had normal children after roentgen therapy. Five patients reported possible abortions in their mates.

Table III

BIOLOGIC EFFECTS OF ROENTGEN RAYS

15 patients received irradiation to include scrotal area	3 patients have had children after roentgen therapy
	5 patients had children, but none after roentgen therapy
	7 patients never had children
19 patients received irradiation, but not to scrotal area	6 patients have had children after roentgen therapy
	8 patients had children, but none after roentgen therapy
	5 patients never had children
3 patients are unmarried	
2 patients did not have roentgen therapy	
39 living patients on whom data were available reported no abnormal children 5 patients reported possible miscarriages	

SUMMARY AND CONCLUSIONS

1. A study of 102 cases of testicular malignant tumors showed the highest incidence to be in the third decade.

2. Analysis of signs and symptoms were not significant in determining prognosis, except for: (a) definite evidence of metastasis; and (b) gynecomastia, which indicates a poor prognosis.

3. A continued postorchiectomy elevation of gonadotropin was usually a bad prognostic sign. The initial height of gonadotropins did not necessarily indicate a fatal outcome as the highest recorded titer occurred in a surviving patient.

4. Gonadotropin studies performed 5 or more years after orchiectomy were generally within normal range—one definitely elevated titer was a castration effect.

5. Seventeen ketosteroid determinations were performed in 25 patients; 20 had normal titers and 5 had slightly decreased titers but these could be the effects of aging. Since part of the ketosteroids are derived from metabolic degeneration of testosterone, one might expect more lower titers in more patients if Leydig cell function had been impaired by irradiation. The 17 hydroxysteroids were performed in 25 patients and none of them showed a decreased titer, which would suggest that adrenal function had not been impaired by irradiation of the abdominal ports (adrenal areas).

6. A careful history of the 39 living patients failed to reveal any abnormalities in the progeny although 5 patients reported possible miscarriages of their spouse. In 15 of these patients radiation therapy included the scrotal area and 3 have had normal children since treatment.

7. Complications of radiation therapy consisted of skin changes which were severe and complicated by development of fibrosarcoma in 1 case; hypertension, probably secondary to radiation nephritis, in another; and aplastic anemia in a third. Leukemia has not been noted in 45 patients surviving 5 to 20 years.

8. The over-all 5 year survival of 102 patients was 50+ per cent. The survival in seminoma (29 patients) was 80 per cent. There were no survivors in choriocarcinoma and the majority died in less than 1 year; 1 died at 26 months.

9. The study shows that in all groups except the choriocarcinoma, death from disease occurred in the period of 16 months following diagnosis. If the patient survived 2 years, death from the tumor was rare.

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MALIGNANT SYNOVIOMA*

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IN AN attempt to clarify the role of radiation therapy in the treatment of malignant synovioma, we have reviewed the records of the Bone Service of the Department of Surgery at Memorial Hospital and have surveyed the pertinent literature. From this study we have attempted to draw guidelines for treatment and have come to the conclusion that in most cases neither radiation therapy alone nor surgery alone offers as good a chance of cure as a combination of the two.

According to Cade,[1] the first case of a tumor arising in a tendon sheath was published by Chassaignac in 1852, and the first case of a "sarcoma arising from synovial membrane" by Salter and Hardie in 1894. Sporadic reports appeared during the next 50 years and in 1944 Haagensen and Stout[3] collected 95 such published cases and added 9 of their own. Their valuable review established the entity of synovial sarcoma, but it also gave the disease such a poor prognosis—only 3 five year "cures" out of 104 cases—that its treatment scarcely seemed worthwhile. In 1950, however, Pack and Ariel[6] reported a 32 per cent 5 year survival rate from the Mixed Tumor Service of the Department of Surgery at Memorial Hospital, and in Cade's personal series the 5 year survival rate as reported in 1962 was 56 per cent.

HISTOLOGIC FEATURES

Synovial tissue has two components, an inner pseudovillous lining and an outer fibrous tissue layer. Its function is the secretion of synovial fluid. In malignant synovioma both components are present and indeed must be demonstrated for the diagnosis to be made. Epithelial-lined clefts are a distinctive feature and are filled with a material actively secreted by the lining cells. This material contains hyaluronic acid, a normal constituent of synovial fluid. The proportionate amounts of each component may vary widely in different tumors and in the primary, recurrent and metastatic manifestations of a single case, but both the epithelial lining and the fibrous tissue layer must be represented for the recognition of malignant synovioma as a distinct entity among the sarcomas of the soft somatic tissues.

Tumors with the histologic features of malignant synovioma are sometimes found in the middle of the thigh or of the arm or other areas where no synovial tissue is normally present. Because of the location away from joints and bursae, the possibility of such a tumor being a synovioma may not be entertained, and it may be lost in the generic limbo of undifferentiated soft part sarcomas. King[4] made a special study of this subject and came to the following conclusions: "The view that synovial tissue can be formed only from special synovial cells is much too rigid an attitude. Given the appropriate stimulus, it seems that connective cells anywhere are capable of this particular kind of differentiation. If we accept this point of view, then the occurrence of synovial tumors in areas away from joints and bursae is easily understandable."

DIAGNOSIS

In the early stages of a malignant synovioma it is unfortunate that there may not be any symptoms or signs suggesting malignancy. In our 38 cases the average duration of the symptoms prior to diagnosis at Memorial Hospital was 4 years, but there

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From the Department of Radiation Therapy and the Bone Service of the Department of Surgery, Memorial Hospital for Cancer and Allied Diseases and James Ewing Hospital of the City of New York, New York.

Table I

A. Age and Sex Distribution at Time of Diagnosis at Memorial Hospital			B. Age Distribution of Cade's[1] 100 Patients
Age	M	F	
0–10		2	10
11–20	1	3	24
21–30	1	1	22
31–40	5	7	15
41–50	5	3	12
51–60	3	3	8
61–70	1	2	5
71–80		1	4
	16	22	100

were 12 cases in which the diagnosis was made within 6 months of onset. Early diagnosis does not always ensure a better prognosis, as in 3 of our cases the whole course from first symptom to death was run in less than 9 months—a degree of malignancy which Cade terms the "hurricane" variety. Neither does late diagnosis necessarily imply a poor prognosis, since a striking natural feature of the disease in some patients is its longevity and chronicity. Nevertheless, the patient's best safeguard is to have a doctor with a high index of suspicion who regards every lump as malignant until proven otherwise—preferably by aspiration biopsy, alternatively by excision and frozen section. An incisional biopsy and packing of the incision until a diagnosis can be made from the paraffin section is unwise and should be avoided.

The roentgenographic findings in synovial tumors have been reviewed by Sherman and Chu.[7] In most cases the picture is that of a soft tissue mass; sometimes there is calcification within the mass and sometimes there is invasion of adjacent bone.

CLINICAL DATA

The records of the Bone Service comprise 38 cases.* At the time when the diagnosis was made at Memorial Hospital the average age was 39 years; the youngest patient was 8 years of age and the oldest 71, but more than half (20/38) were between 30 and 50 years of age. There were 16 males and 22 females (Table I), 37 white and 1 Negro. As regards the site of the primary tumor, the foot, with 11 cases, was the commonest location; then the knee (7), hip (4), ankle (3), forearm (3), elbow (2), buttock (2), and 1 instance each in the finger, hand, wrist, shoulder, thigh and symphysis pubis. The 3 forearm, 2 buttock and 1 thigh tumors were noted as examples of synovioma arising in locations normally devoid of synovial tissue. In Haagensen and Stout's 104 cases the average age was 32 years, males predominated 3:2, and 79 per cent of their tumors occurred in the lower extremity with 21 per cent in the upper extremity. In Cade's 100 cases, 56 were under 30 years of age and 27 were between 30 and 50 years old; males predominated 71:29; 49 per cent occurred in the lower limb, 41 per cent in the upper limb and 10 per cent in other sites.

In Table II the summary of our 38 cases is presented in 5 subgroups: the first contains 8 patients who are living and free of disease for more than 5 years from the time of diagnosis at Memorial Hospital; the second contains 7 cases surviving for more than 5 years from the date of diagnosis at Memorial Hospital but which are now dead, 6 from malignant synovioma and 1 from myocardial infarction: the third subgroup lists 9 cases dead in less than 5 years from the date of diagnosis, all from malignant synovioma; the fourth subgroup lists the 9 patients who already had distant metastases on entry to Memorial Hospital, all dead; and the last subgroup contains the 5 patients treated less than 5 years ago, all of whom are still living.

TREATMENT

Wide excision is now the accepted minimal treatment for sarcoma of the soft somatic tissues and its value in malignant synovioma when combined with irradiation

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* The authors are greatly indebted to Dr. R. V. Hutter for review of the pathologic material and confirmation of the diagnosis in all 38 cases.

Table II

No.	Age at Diagnosis at Memorial Hospital	Sex	Site	Length of Symptoms before Diagnosis at Memorial Hospital	Year of Diagnosis at Memorial Hospital	Previous Treatments and Initial Treatment at Memorial Hospital	Follow-Up
A. *Patients Surviving More Than 5 Years after Diagnosis at Memorial Hospital*							
114304 Case 1	35	F	Knee	8 years	1934	Local excision and postoperative roentgen therapy, 4,000 r tumor dose	Alive and well 28 years
105408 Case 2	31	F	Elbow	6 months	1949	4 roentgen treatments to mass elsewhere, then local excision at Memorial Hospital	Alive and well 13 years
106638 Case 3	9	F	Forearm	2 months	1952	Local excision elsewhere; wide excision at Memorial Hospital	Alive and well 10 years
106851 Case 4	40	F	Foot	8 years	1956	Local excision elsewhere; 3 weeks later below-knee amputation at Memorial Hospital	Alive and well 6 years
116201 Case 5	39	F	Foot	7 months	1949	Two local excisions elsewhere 1948, 1949; below-knee amputation at Memorial Hospital	Alive and well 13 years
121959 Case 6	43	M	Wrist	29 years with pea size nodule which began to enlarge 6 wk. prior to admission	1955	Local excision elsewhere; above-elbow amputation at Memorial Hospital; recurrence in 1961 at lateral border of axilla; interscapulo-thoracic amputation and postoperative radiation therapy performed elsewhere	Alive and well 7 years
125925 Case 7	41	M	Knee	3 years	1955	Local excision elsewhere; subtrochanteric amputation at Memorial Hospital	Alive and well 7 years
119612 Case 8	14	F	Hip	1 month	1954	Local excision elsewhere; wide excision at Memorial Hospital	Alive and well 8 years
B. *Patients Surviving More Than 5 Years after Diagnosis at Memorial Hospital, Then Dying of Tumor or Intercurrent Disease*							
107524 Case 9	61	F	Region of pubic symphysis	7 years	1955	Two local excisions elsewhere; local excision at Memorial Hospital	Died of disease 1960; 5 years
410203 Case 10	41	F	Hip	1 year	1937	Local excision elsewhere in 1936; June, 1937, roentgen therapy for recurrence at Memorial Hospital, 5,200 r tumor dose plus 11 mc radon seeds into lymph node; 1945 fracture of femur; May, 1954 pulmonary metastases	Died of disease 1954; 17 years
136681 Case 11	53	M	Foot	2 months	1953	Local excision elsewhere; below-knee amputation at Memorial Hospital	Died of disease 1960; 7 years
450153 Case 12	20	F	Ankle	3 years	1942	Biopsy elsewhere; below-knee amputation at Memorial Hospital	Died of disease 1952; 10 years
119638 Case 13	52	M	Foot	1 year	1951	Local excision and roentgen therapy elsewhere; below-knee amputation at Memorial Hospital	Died of myocardial infarction 1960 without evidence of tumor; 8 years
130947 Case 14	47	M	Forearm	7½ years	1953	Wide excision elsewhere; recurrence above operative scar 3½ years later, interscapulo-thoracic amputation at Memorial Hospital	Died of disease 1958; 5 years

TABLE II (*Continued*)

No.	Age at Diagnosis at Memorial Hospital	Sex	Site	Length of Symptoms before Diagnosis at Memorial Hospital	Year of Diagnosis at Memorial Hospital	Previous Treatments and Initial Treatment at Memorial Hospital	Follow-Up
133166 Case 15	8	F	Foot	7½ years	1951	3 local excisions since age 1½ elsewhere; 1951 local excision at Memorial Hospital; 1954 bilateral pulmonary metastases; roentgen therapy	Died of disease 1959; 8 years

C. *Patients Surviving Less Than 5 Years after Diagnosis at Memorial Hospital*

No.	Age at Diagnosis at Memorial Hospital	Sex	Site	Length of Symptoms before Diagnosis at Memorial Hospital	Year of Diagnosis at Memorial Hospital	Previous Treatments and Initial Treatment at Memorial Hospital	Follow-Up
119077 Case 16	16	M	Ankle	3 years	1957	2 local excisions elsewhere, 1954, 1957; below-knee amputation at Memorial Hospital	Died of disease; 10 months
240278 Case 17	53	M	Hip	2 years	1961	Hemipelvectomy	Died of disease; 2 years
156463 Case 18	45	M	Finger	36 years	1949	Many procedures over many years starting in 1916 after 3 years of symptoms; interscapulo-thoracic amputation at Memorial Hospital	Died of disease; 3 years
Roll 35—1936 Case 19	35	M	Shoulder	1 year	1936	Interscapulo-thoracic amputation	Died of disease; 3 years, 3 months
220400 Case 20	15	F	Buttock	3 months	1960	Incomplete excision elsewhere; hemipelvectomy at Memorial Hospital	Died of disease; 1 year
Roll 35—1938 Case 21	55	F	Knee	1 month	1938	Excision and postoperative roentgen therapy elsewhere; roentgen therapy to primary site at Memorial Hospital; subsequent above-knee amputation elsewhere	Died of disease; 1 year
123278 Case 22	63	F	Foot	4 years	1956	2 excisions elsewhere; wide excision at Memorial Hospital followed by supracondylar amputation 5 months later	Died of disease; 2 years, 6 months
131662 Case 23	40	M	Hand	4 months	1955	Interscapulo-thoracic amputation because of positive epitrochlear lymph nodes	Died of disease; 3 years, 6 months
410014 Case 24	31	M	Knee	1½ years	1952	Local excision elsewhere; mid-thigh amputation at Memorial Hospital	Died of disease; 1 year

D. *Patients Entering Memorial Hospital with Metastases*

No.	Age at Diagnosis at Memorial Hospital	Sex	Site	Length of Symptoms before Diagnosis at Memorial Hospital	Year of Diagnosis at Memorial Hospital	Previous Treatments and Initial Treatment at Memorial Hospital	Follow-Up
235042 Case 25	71	F	Knee	2 months	1960	High thigh amputation 1959 elsewhere; recurrence in stump and pulmonary metastases; radiation therapy to both areas	Died of disease; 4 months
220678 Case 26	52	F	Ankle	3 years	1962	3 local excisions plus radiation therapy elsewhere; pathologic fracture in femur and pulmonary metastases	Died of disease; 1 month
Roll 35—1 Case 27	40	M	Knee	3 years	1946	3 local excisions plus radiation therapy elsewhere; recurrent and pulmonary metastases; radiation therapy to both areas	Died of disease; 9 months
Roll 17—1947 Case 28	20	F	Foot	3–4 years	1947	Multiple excisions and radiation therapy elsewhere; below-knee amputation at Memorial Hospital for ulcerated painful tumor	Died of disease; 1 year, 8 months
240224 Case 29	34	M	Buttock	2 months	1961	Radiation therapy to primary lesion and both lung fields	Died of disease; 2 months

Table II (*Continued*)

No.	Age at Diagnosis at Memorial Hospital	Sex	Site	Length of Symptoms before Diagnosis at Memorial Hospital	Year of Diagnosis at Memorial Hospital	Previous Treatments and Initial Treatment at Memorial Hospital	Follow-Up
400012 Case 30	47	F	Foot	4–5 years	1951	Local excision 3 years prior to admission; radiation therapy 1 year prior to admission elsewhere; below-knee amputation at Memorial Hospital because of pain in tumor	Died of disease; 1 year
Roll 35—1940 Case 31	25	M	Hip	1 year	1940	Biopsy elsewhere; radiation therapy to primary tumor at Memorial Hospital	Died of disease; 1 year
Roll 17—1941 Case 32	48	F	Thigh	1 month	1941	Radiation therapy to metastases in femur	Died of disease; 8 months
460436 Case 33	44	M	Foot	1 year	1951	Below-knee amputation; thoracotomy for solitary middle lobe metastasis	Died of disease; 1 year, 6 months

E. *Patients Treated Less Than 5 Years Ago Still Living*

No.	Age at Diagnosis at Memorial Hospital	Sex	Site	Length of Symptoms before Diagnosis at Memorial Hospital	Year of Diagnosis at Memorial Hospital	Previous Treatments and Initial Treatment at Memorial Hospital	Follow-Up
230539 Case 34	31	F	Foot	1 month	1961	2 local excisions and radiation therapy elsewhere; wide excision at Memorial Hospital	Living and well; 1 year, 6 months
243714 Case 35	47	F	Foot	8 years	1962	Local excision elsewhere 1 month prior to admission; below-knee amputation at Memorial Hospital	Living and well; 1 year
243718 Case 36	36	F	Forearm	20 years	1962	Local excisions of lesion on forearm, 20 years, 5 years and 8 weeks prior to admission; mid-humeral amputation at Memorial Hospital	Living and well; 1 year
239591 Case 37	34	F	Knee	1 year	1961	Local excision elsewhere 7 days prior to admission; hip-disarticulation at Memorial Hospital	Living and well; 1 year, 6 months
242020 Case 38	64	M	Elbow	6 months	1962	Local excision elsewhere; radiation therapy to primary lesion at Memorial Hospital because of "suspicious nodule" on chest roentgenogram	Living and well with suspicious chest study; 1 year

is demonstrated by the 56 per cent 5 year survival rate in Cade's personal series of cases. Of our 38 cases only 7 received their first treatment at Memorial Hospital; 3 of these 7 presented with metastases and died in 2 months, 8 months and 18 months, respectively. Three underwent amputation but died of malignant synovioma in 2 years, 3 years and 3½ years, respectively. The seventh patient was treated by local excision and postoperative irradiation and is alive and well 28 years later.

Procedures which the remaining 31 cases underwent prior to being referred to Memorial Hospital are listed in Table III, and also the first procedure at Memorial Hospital for the 25 of those 31 cases who had no evidence of metastases on admission. Whereas there was only 1 initial amputation in the 31 cases prior to their referral, amputation was the initial treatment in Memorial Hospital in 15 cases. Of these 15 amputations, in 11 an intended complete excision had been done in other hospitals;

TABLE III

COMPARISON OF INITIAL PROCEDURES BEFORE REFERRAL AND AFTER ADMISSION TO MEMORIAL HOSPITAL

Procedure	Before Referral	After Admission*
Biopsy Only	2	0
Local Excision	14	3
Repeated Local Excisions	5	0
Wide Excision	1	4
Amputation	1	15
Radiation Therapy Only	1	2
Local Excision and Postoperative Radiation Therapy	2	1
Repeated Local Excisions and Radiation Therapy	5	0
Total	31	25

* Excluding 6 cases with distant metastases.

residual tumor was found in the amputated specimen in 7 cases, and no residual tumor was found in the other 4. A further analysis of those with residual tumor shows that the primary lesion was in the foot in 3 instances and the ankle and the wrist in 1 case each; in these sites it is generally recognized that a complete excision of a sarcoma is virtually impossible and that primary amputation is the procedure of choice.

Radiation therapy was the sole treatment of the primary tumor only in the 4 patients presenting with distant metastases. Irradiation was also used for the treatment of metastases in 12 patients, the majority of whom had worthwhile palliation for a short time and, in 1 patient, for 4 years (Table IV). An example of pulmonary metastases with an excellent response to irradiation is illustrated in Figure 1, *A* and *B;* and 2, *A* and *B*.

RESULTS OF TREATMENT

There are 24 patients who entered Memorial Hospital without evidence of distant metastases more than 5 years ago and 15 or 62 per cent survived for more than 5 years. The 5 year disease-free survival rates are 33 per cent in our series, 50 per cent in Cade's series and 26 per cent in the series reported by Pack and Ariel (Table V). Too much emphasis, however, should not be placed on the percentages, for malignant synovioma is a rare tumor. What should be emphasized is that aggressive treatment of this disease is absolutely worthwhile.

From the clinical data in Table II, a picture of the course of malignant synovioma may be obtained by adding together the duration of symptoms before diagnosis and the length of life after diagnosis. For the 8 patients still living and well, their average age at the time of diagnosis was 31 years, their average duration of symptoms prior to diagnosis was 6 years and their average survival since diagnosis is 11 years—making the total duration 17 years so far. For the 7 patients who survived more than 5 years but have since died, their average age at the time of diagnosis was 40 years, the average length of symptoms before diagnosis was 4 years and the average length of life after diagnosis was 9 years, making the total duration 13 years. For the 9 patients who lived less than 5 years the average age was 40 years, the duration of symptoms prior to diagnosis was 5 years, and the average life after diagnosis was 2 years, making a total duration of 7 years. The 9 cases entering Memorial Hospital with distant metastases averaged 42 years old, had

TABLE IV

SITE OF METASTASES TREATED BY IRRADIATION

Site	No. of Each Site Treated	Objective Regression	Subjective Relief
Lung	9	8	8
Bone	4	Not recorded	4
Brain	1	Not recorded	1
Soft Tissue	2	2	2
Stump Recurrence	1	1	1

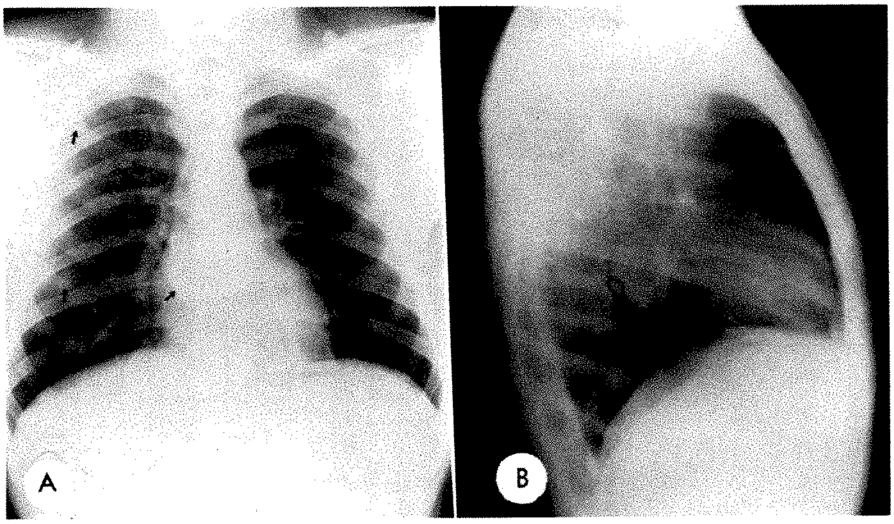

Fig. 1. (*A* and *B*) Chest roentgenograms made on November 6, 1957. Patient received radiation therapy to the right hemithorax from November 18 to December 3, 1957, a tumor dose of 2,035 r. The left hemithorax received a tumor dose of 2,000 r from December 26, 1957 to January 6, 1958.

had symptoms for an average of 2 years and lived an average of only 8 months after diagnosis.

DISCUSSION OF IRRADIATION

In Pack and Ariel's report all of their 9 cases, alive and free of disease for 5 years or more, were treated by combined surgery and radiation therapy. Cade states that "... surgery, however extensive, does not, and in fact cannot give as effective control as a combination of surgery and radiation therapy. This is fully supported by the studies of Pack and Ariel and of Lichtenstein."

A 35 year old female (Case 1) gave an 8 year history of a tumor of the knee; local excision was done and postoperative roentgen therapy was given in 1934 and she remains well for over 28 years; the estimated tumor dose was 4,000 r. A 41 year old female (Case 10) had in 1936 local excision of a tumor of the hip which she had noticed for a year; it soon recurred and she was

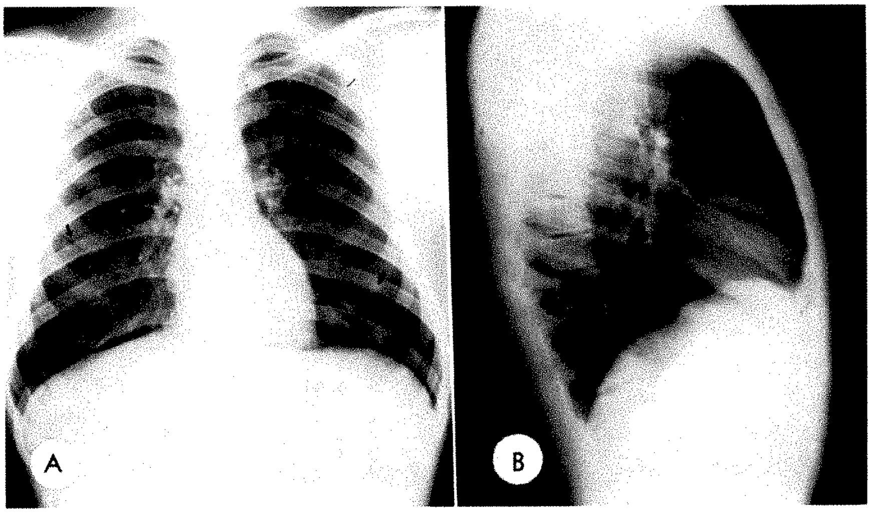

Fig. 2. (*A* and *B*) Chest roentgenograms made on January 6, 1958.

TABLE V

Series	No. of Patients	5 Year Survival		5 Year Disease Free Survival	
		(no.)	(per cent)	(no.)	(per cent)
Cade[1]	46	26	56	23	50
Pack and Ariel[6]*	34	11	32	9	26
Bone Service* Memorial Hospital	24	15	62	8	33

* Excluding patients with distant metastases when first seen.

given 200 kv. roentgen therapy in June, 1937 (5,200 r tumor dose). In addition, an inguinal lymph node metastasis was implanted with gold radon seeds (11 mc total). The patient then remained clinically free of disease for 17 years, although she sustained a fractured femur in 1945, which was recorded, but not verified, as due to "radiation osteitis;" in May, 1954 she was found to have pulmonary metastases and she died in December 1954. Case 21 had noticed a tumor of the knee for only 1 month; it was excised and postoperative irradiation was given elsewhere, and then more irradiation was given at Memorial Hospital when the patient refused amputation; a little later, however, amputation was done in another hospital, but was unsuccessful and the patient died within the year. There were also 4 cases (Cases 27, 29, 31, and 38) with pulmonary metastases in which the primary tumor was irradiated. The effectiveness of radiation in metastatic malignant synovioma has already been mentioned.

If the value of postoperative irradiation is becoming more widely appreciated, we would add two suggestions; first, that supervoltage roentgen rays or telecurie therapy be used, so that a tissue dose of 5,000–6,000 r can be given with minimal risk of "radiation osteitis" or other late radiation damage. Second, we think that preoperative irradiation is both more logical and more effective than postoperative; more logical, because its cancerostatic effect makes operative manipulations safer, and because regression of the tumor makes its boundaries better defined; more effective, because the microscopic nests of tumor cells occurring at various distances from the main mass of the tumor are more readily destroyed while their blood supply is intact than in the devascularized postoperative field.

CONCLUSION

From our study of 38 cases of malignant synovioma referred to the Bone Service at Memorial Hospital and from a review of the literature we have drawn the following conclusions:

1. Although the natural duration of the disease is highly variable, in 50 per cent of cases it is not less than 5 years.
2. Wide local excision and postoperative irradiation is the present treatment of choice, but the value of preoperative irradiation merits consideration.
3. For tumors in the foot, ankle, hand and wrist, a below-knee or below-elbow amputation is preferable.
4. A 50 per cent disease-free 5 year survival rate is usually obtainable by a combination of surgery and radiation therapy.

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MANAGEMENT AND SURVIVAL OF 883 PATIENTS WITH MALIGNANT LYMPHOMA*

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A UNIQUE experience in treating 883 patients with malignant lymphomas, in which relatively few physicians have outlined the therapy and followed the disease during its natural history, is described in this report. Five hundred and sixty-seven patients with lymphosarcoma and 316 patients with Hodgkin's disease have been treated at the Pack Medical Group from 1945 through 1957.

The sex and age of the patients at the clinical onset of the disease are presented in Figure 1. The conventional classification of Peters,[3] as shown in Table I, which describes the stage of disease present when the patient is first seen, was used.

All of the pathologic material was reviewed and classified by Dr. George K. Higgins. Morphologically, the lymphosarcomas are subdivided into: (1) giant follicular sarcoma (Brill-Symmers disease); (2) lymphosarcoma (small cell type); and (3) reticulum-cell sarcoma. Patients with Hodgkin's disease are classified as having Hodgkin's paragranuloma, granuloma, or sarcoma. Table II shows the distribution of the patients according to stage and classification of the disease.

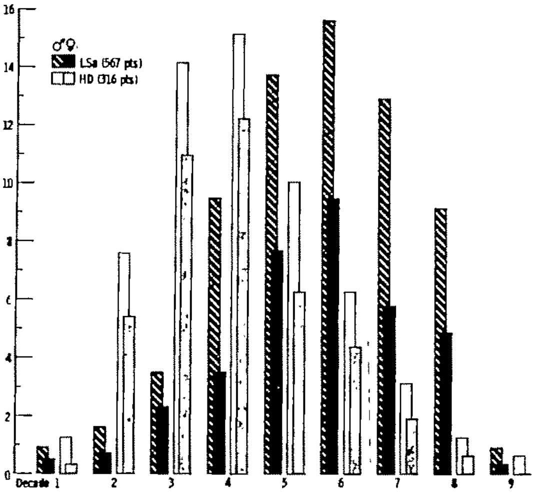

FIG. 1. Distribution of lymphosarcoma and Hodgkin's disease according to the age of the patients at the clinical onset of the disease and their sex.

PRINCIPLES OF TREATMENT

TREATMENT OF PATIENTS WITH STAGE I MALIGNANT LYMPHOMA: SURGERY AND IRRADIATION

The various methods of treatment are listed in Table III. In selected patients with unicentric disease, surgery is the preferred initial method of treatment when the disease is found: (1) in the upper third and middle third of the neck; (2) in the lower half of the axilla; (3) in the femoral fossa and superficial inguinal lymph nodes; (4) as a primary focus in any portion of the gastrointestinal tract; and (5) as a primary focus in any single organ. Eight patients were treated by radical neck dissection; 6 by radical axillary dissection; and 16 by radical groin dissection. The surgical procedures and end results for this group are summarized in Table IV. Postoperative irradiation is given routinely to these patients.

In the postoperative radiation therapy of those patients who have had radical neck or groin dissections, the factors include: 250 kv.; 50 cm. target skin distance; 1.5 mm. Cu filter; daily fractional increments of 250 r; a total tumor dose of 3,000 to 3,600 r, depending on skin tolerance. Postoperative radiation therapy is given similarly to those patients having radical axillary dissections.

Following laparotomies, patients are given irradiation, employing a 250 kv. machine and 70 cm. target skin distance with fractions of 300 r daily, alternating between an anterior and a posterior port. Generally, 3,000 or 3,600 r is given to the region involved.

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From the Pack Medical Foundation, New York, New York.

The majority of patients with Stage I malignant lymphoma are treated initially with a tumor dose of radiation. Following biopsy and wound healing, a generous port is outlined to cover adequately the region involved. Factors include a 250 kv. machine, 3,000 or 3,600 r in air (depending on skin tolerance), given to each involved region; generally 250 to 300 r daily. In the present series, 104 patients with lymphosarcoma and 62 patients with Hodgkin's disease have been treated in this manner.

TREATMENT OF PATIENTS WITH STAGE II MALIGNANT LYMPHOMA

There were 311 patients with Stage II lymphosarcoma and 188 patients with Stage II Hodgkin's disease in this series. Radiation therapy is the principal form of treatment for this group. In those patients in whom constitutional symptoms are present, chemotherapy is used as an adjuvant to control sweating, malaise, and pruritus. Hormonal therapy is used to control hemolytic anemia or to obtain a lympholytic effect in patients with lymphosarcoma as well as a stimulating effect on the bone marrow.

Following diagnosis, the involved regions are outlined with generous ports to encompass the regional lymph nodes; using a 250 kv. machine, 2,000 to 2,400 r in air is given as a total dose to each involved region. The total dose is individualized for each patient each day, depending on tolerance and the condition of the skin. Two hundred and fifty to 300 r may be given daily if the patient is in good condition, whereas 150 to 200 r may be chosen if the patient's general health is poor. Two ports may be paired (*e.g.*, a mediastinal port and a groin port) if multiple ports are being treated. No more than 400 r is given as a total dose per day.

For the neck and the axillary and groin regions, a 50 cm. target skin distance is generally chosen. A 70 cm. target skin distance is used for the mediastinum, para-aortic lymph nodes, and abdominal region. If a greater depth dose is desired, at times even a 100 cm. target skin distance is used in a hypersthenic, thick-chested person for a mediastinal or large abdominal port.

Management of Side Effects of Radiation Therapy. If the platelet count is depressed below 75,000 per cu. mm., radiation

Table I

CLASSIFICATION OF MALIGNANT LYMPHOMA

Stage I	Unicentric disease
Stage II	Regional disease; constitutional symptoms may be present
Stage III	Generalized disease; generally with constitutional symptoms

Table II

DISTRIBUTION OF PATIENTS WITH MALIGNANT LYMPHOMA ACCORDING TO STAGE AND CLASSIFICATION

	Lymphosarcoma	Hodgkin's Disease
Stage I	146	74
Stage II	311	188
Stage III	110	54
Total	567	316

Table III

MODALITIES OF TREATMENT IN MALIGNANT LYMPHOMA

A. Radiation Therapy
  1. Definitive in Stage I
  2. Possibly definitive in Stage II
  3. Palliative in Stage III
B. Surgery
  1. Definitive in selected patients with unicentric disease
  2. Palliative; for example, to remove bulky tumor masses or relieve intestinal obstruction
C. Chemotherapy (adjuvant)
  1. Alkylating agents
  2. Antimetabolites
  3. Hormones
D. Combinations of the above

TABLE IV

SURGICAL TREATMENT OF UNICENTRIC MALIGNANT LYMPHOMA
5 YEAR SURVIVALS

Procedure	No. of Patients	5 Year Survivals	
		No.	Per Cent
Lymphosarcoma			
Radical dissection			
Neck	5	3	60.0
Axillary	3	2	66.6
Groin	11	8	72.7
Subtotal gastric resection	5	3	60.0
Total gastric resection	4	2	50.0
Segmental excision, small intestine	6	3	50.0
Splenectomy	1	0	0
Appendectomy	1	1	100.0
Hysterectomy	1	1	100.0
Resection, portion of large bowel	2	2	100.0
Segmental excision, lung	2	0	0
Segmental hepatic lobectomy	1	1	100.0
Total	42	26	62.0
Hodgkin's Disease			
Radical dissection			
Neck	3	2	66.6
Axillary	3	2	66.6
Groin	5	4	80.0
Segmental excision, lung	1	0	0
Total	12	8	66.6

therapy may have to be limited or used intermittently. The white blood cell count may decrease to 1,000 or 2,000, and patients are treated when the white blood cell count is above 1,500. Nausea and vomiting, which occur in about one fourth of the patients, are controlled with tigan in 200 mg. doses, or compazine, in 10 mg. doses. Pyridoxine, 50 mg., 1 hour prior to therapy, may also be helpful. Unusual sensitivity to the phenothiazine group of drugs must be watched for carefully. The hemoglobin, white blood cell count and platelets are determined periodically, and therapy is temporarily discontinued if the white blood cell count is below 1,500 or the platelet count below 75,000. Whole-blood transfusions are used to restore the hemograms toward normal and lessen the possibility of bleeding or infection.

Chemotherapy and Hormonal Therapy. In general, the constitutional symptoms are controlled with chemotherapy and hormonal therapy. All patients are carefully assessed prior to the initiation of chemotherapy. This includes a bone marrow aspiration or a biopsy if it is indicated. The details of this aspect of treatment have been described previously by the authors.[1,2]

Uric acid levels are periodically determined, and adequate hydration is maintained to prevent the complication of uric acid nephropathy, particularly when massive, bulky disease is present.

TREATMENT OF PATIENTS WITH STAGE III MALIGNANT LYMPHOMA

There were 110 patients with Stage III lymphosarcoma and 54 patients with Stage

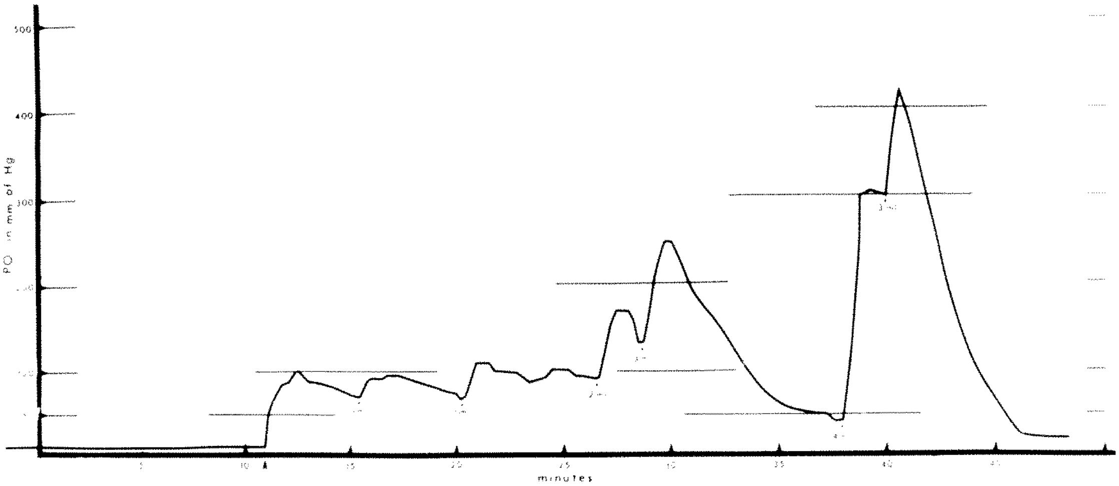

FIG. 1. Graph showing muscle pO_2 build-up in rabbit muscle (—) during arterial infusion of hydrogen peroxide (H_2O_2). 1 = ml. of H_2O_2.

had been only partially successful. At this time he had a severe ulcer of his right foot of several months' duration, which had proven resistant to all forms of therapy. A catheter was placed into his right femoral artery, and 250 cc. of .24 per cent hydrogen peroxide solution was infused into the extremity, twice a day for two weeks (Fig. 3). Four weeks later the foot was completely healed (Fig. 4). The patient received no other form of treatment. The foot has remained completely healed despite normal

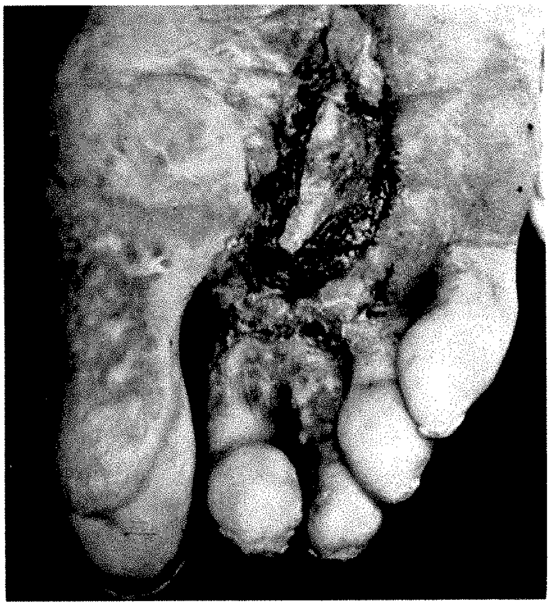

FIG. 2. Photograph of right foot of an 18 year old boy, who received overexposure of radiation. Appearance before H_2O_2 infusion therapy.

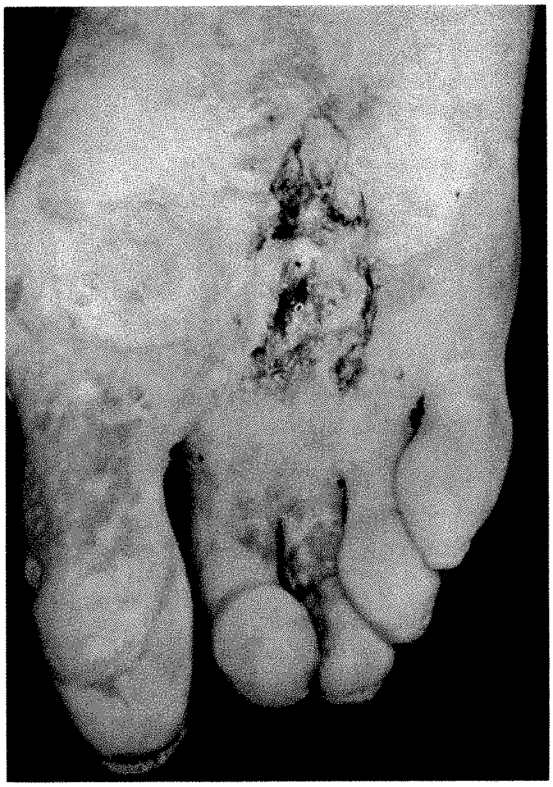

FIG. 3. Same as in Figure 2, two weeks after completion of H_2O_2 infusion therapy. Patient received no other form of treatment.

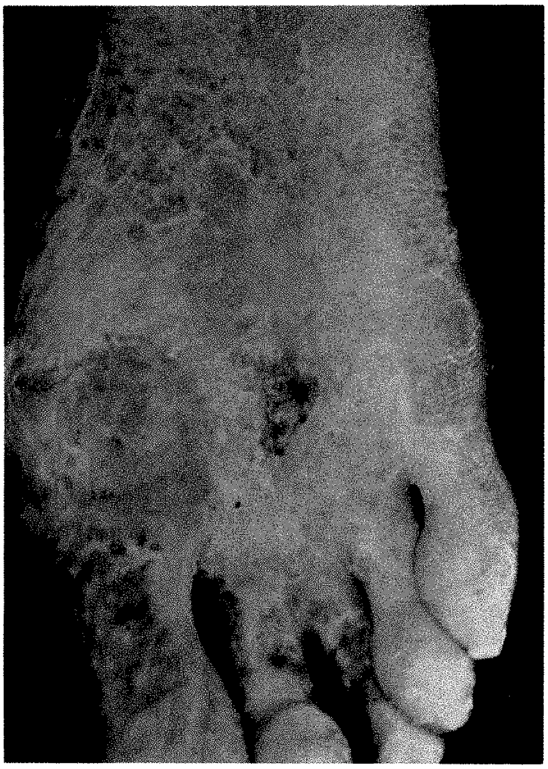

FIG. 4. Same as in Figures 2 and 3, one month after completion of H_2O_2 infusion therapy.

weight bearing. Other cases such as this have also demonstrated the tissue effect of intra-arterial hydrogen peroxide.

During the past $2\frac{1}{2}$ years, we have used intra-arterial regional oxygenation utilizing hydrogen peroxide in 137 patients. However, this number includes, in addition to the radiation series, many other areas, such as chemotherapy, isotopes, cardiac studies, shock, burns, marrow depletion, atherosclerosis, wound healing, etc. Much of the information gained during this period has been published,[3,6,10–12] and some has been scheduled for presentation.[5,7]

This paper will deal with a summary of the knowledge gained in regard to this technique when utilized with external radiation in the treatment of malignant tumors in humans.

TECHNIQUE

Our technique, stated very briefly, is placing and securing a 5 French polyvinyl catheter into the desired artery under direct surgical vision. The catheter is checked repeatedly with 2 per cent sodium fluorescein, and on occasion by contrast studies. In addition, we keep our catheters filled with heparin and heat sealed, except during the period of infusion. The only arterial branches we use at present are the: (1) external carotids; (2) common carotids; (3) brachials; (4) aorta; and (5) femorals.

Vessels smaller than these should be avoided, especially the vertebrals. The head and neck are treated by the carotids. The chest, abdomen, or pelvis is treated by placing the catheter at different levels in the aorta. We use the celiac axis and renals only in select cases. A detailed report of technique is in preparation.[5]

As a result of our improved technique we can treat approximately 85 per cent of the patients on an outpatient basis. This makes it possible to treat all of our patients daily, utilizing conventional protracted radiation therapy. Our well-trained team using high output radiation treats 4 to 6 patients an hour.

NORMAL TISSUE TOLERANCE

During the first year and one-half of our study, we limited the radiation dosage to 85 per cent of standard acceptable techniques employed in our department. We have used 100 per cent of our standard doses utilizing standard protraction therapy since June, 1963. We have treated through cartilage, bone invasion and osteomyelitis. As of this date we have not experienced radiation morbidity; of course, it is recognized that it is too early to evaluate late radiation injury. In addition and more significantly, no increase in normal tissue reaction has been observed.

TISSUE REPAIR

We have found that in many patients normal tissue repair has been markedly accelerated.[5,11,12] Biopsy specimens show normal tissue repair as early as 4 days following the beginning of irradiation, while tumor damage is progressing at the same time.

COMPLICATIONS

The complications we have experienced using this technique appear to be twofold: (1) those associated with catheter techniques; and (2) those specifically due to the hydrogen peroxide.

The complications which occur due to catheter techniques are rapidly being overcome by improvements in technique and management, and are now in the acceptable range.

The only complication which can occur using hydrogen peroxide itself is the production of severe arteriospasms. These can be severe enough to produce infarction and shock. Individual variation of flow rate, careful observation during infusion, and the adequate use of vasodilators, such as tolazoline (Priscoline) can prevent this effect. A detailed report on possible complications and how to avoid them is now being prepared for publication.[5]

RESULTS

The number of variables involved to date has precluded a statistically designed prospective study. Specific individual patient responses have been encouraging, although only long term cure rates with adequate controls can prove the validity and applicability of this technique.

Out of the number of surviving patients treated at least 1 year ago, 8 are well and demonstrated what we considered objective gross improvement in the radiotherapeutic ratio.

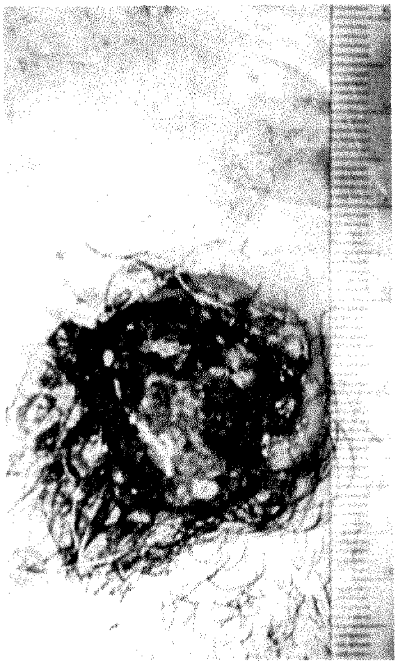

Fig. 5. Case 1. Grade II squamous cell carcinoma of right cheek. Appearance before therapy.

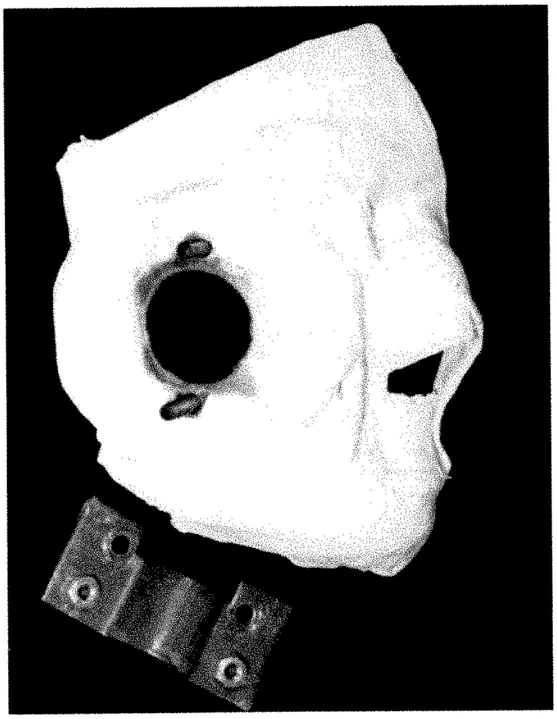

Fig. 6. Case 1. Mask showing outline of area to be treated. Reversible bar not in position.

ILLUSTRATIVE CASES

Case 1. An 88 year old white male had a Grade II squamous cell carcinoma of the right cheek (Fig. 5). The catheter was placed into the right external carotid artery. A mask was used to bisect the lesion (Fig. 6, 7 and 8). The nasal half received 200 r daily, then the infusion started and the auricular half received 200 r daily. Seven days later, each half had received 1,000 r. The biopsy across the bisecting line showed viable appearing tumor anteriorly and no tumor posteriorly with evidence of tissue healing (Fig. 9). Therapy was continued as before. A total of 10 days from inception, the posterior half was completely epithelized up to

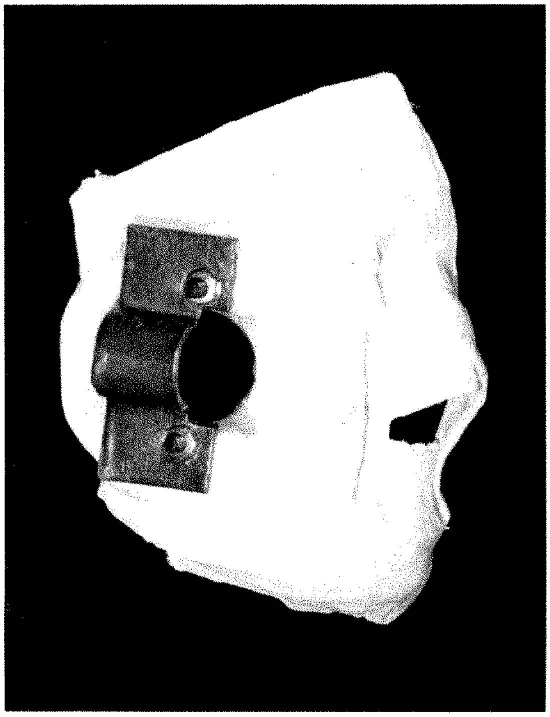

Fig. 7. Case 1. Bar in position to treat nasal half of lesion.

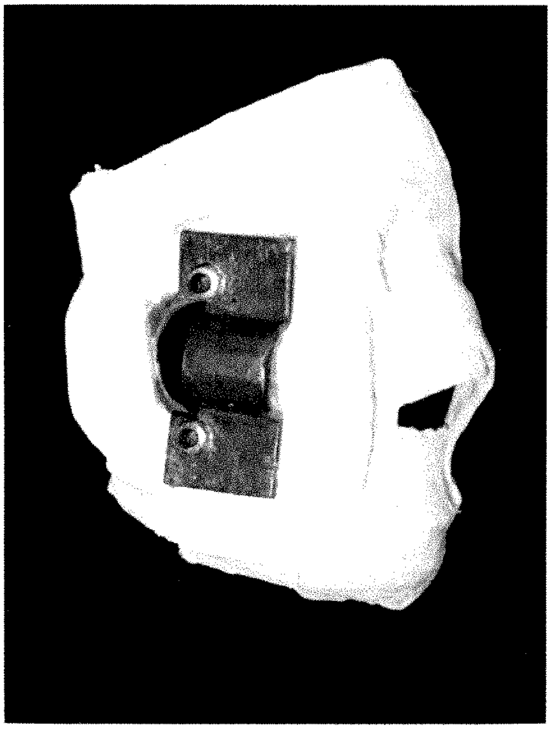

Fig. 8. Case 1. Bar in position to treat auricular half of lesion.

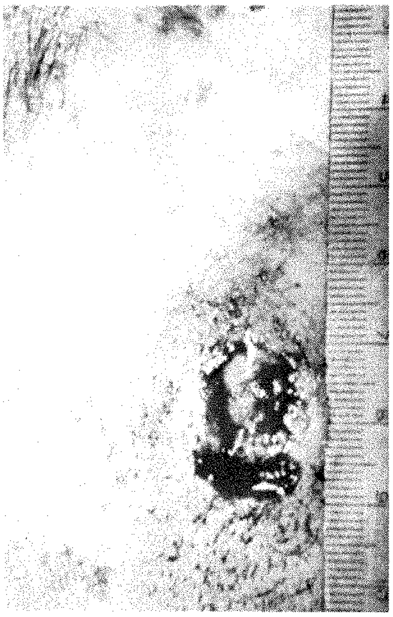

Fig. 9. Case 1. Appearance at 7 days and 1,000 r. Note biopsy site across bisection line.

the bisecting line (Fig. 10). After each half had received 1,887 r, the nasal half was given a single dose of 1,200 r in order to give a full therapeutic dose. No other treatment was given to the auricular half. Figure 11 demonstrates the appearance of the lesion 6 months later. The patient is alive and well today, $2\frac{1}{2}$ years later.

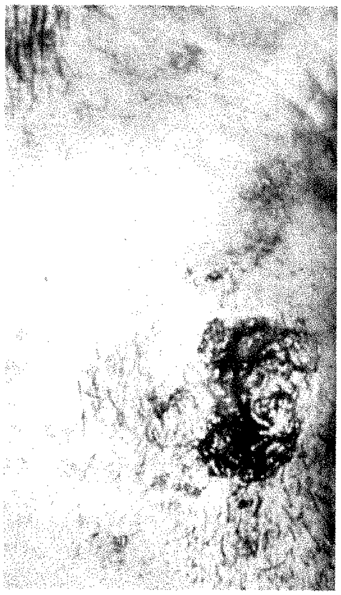

Fig. 10. Case 1. Appearance at 10 days. Note complete healing of auricular half and viable appearance of nasal half.

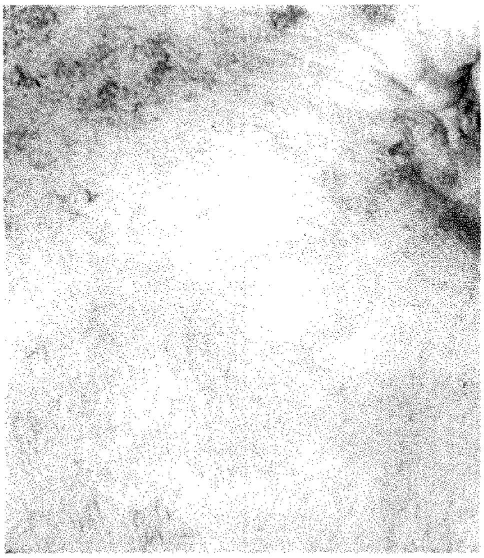

Fig. 11. Case i. Appearance 6 months later. There is complete healing of the lesion.

Case ii. A 62 year old white male had a Grade ii squamous cell carcinoma of the entire lower lip, the left angle of mouth and up on to the extreme left upper lip (Fig. 12). The catheter was placed into the left external carotid artery. Dye studies showed no distribution to the right lip. Infusion of hydrogen peroxide daily for 1 week showed no apparent effect upon any part of the lesion (Fig. 13). A mask was built (Fig. 14, 15 and 16); the patient's right area of the lip received 200 r daily with no infusion, the mid area received the same dosage with the infusion following the irradiation, and the left area received 200 r during the infusion. After receiving 11 treatments of 200 r each, the left area was healed. No further therapy was given. The right and mid areas after receiving 3,000 r (Fig. 17) were still viable. Therapy was continued on the right and mid areas until they had received 6,000 r in 6 weeks. Five months later the lip was totally healed (Fig. 18). This patient is alive and well today, 2 years after treatment and has received no further therapy.

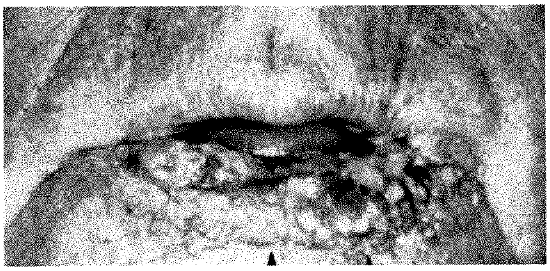

Fig. 12. Case ii. Grade ii squamous cell carcinoma of entire lower lip, left angle of mouth and left end of upper lip, before treatment.

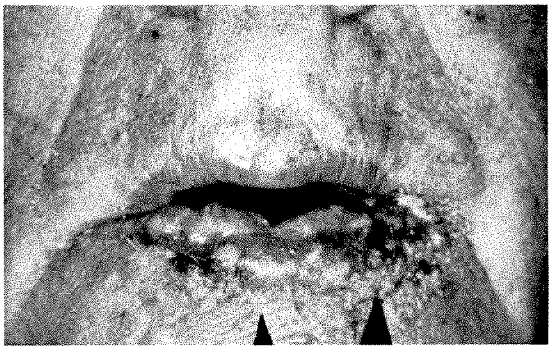

Fig. 13. Case ii. After 1 week of hydrogen peroxide infusion to the left lip only, no change is noted.

Case iii. A 29 year old white male had had a left lower lip and alveolar ridge resection with a left radical neck dissection 2 years previously. He did not return for follow-up examinations. He returned on June 4, 1962 and had a 48 sq. cm. fungating mass under the jaw with fixation of the tongue, necrosis, a pin extending from the mandible into the large defect and osteomyelitis of the jaw (Fig. 19). A catheter inserted into the right common carotid artery gave excellent distribution of the infusion throughout the entirety of the lesion. Two million volt roentgen therapy was given concurrently with hydrogen peroxide infusion. Using simple opposing fields, 4,500 rads were delivered in 3 weeks (14 treatments). No further treatment was given. In

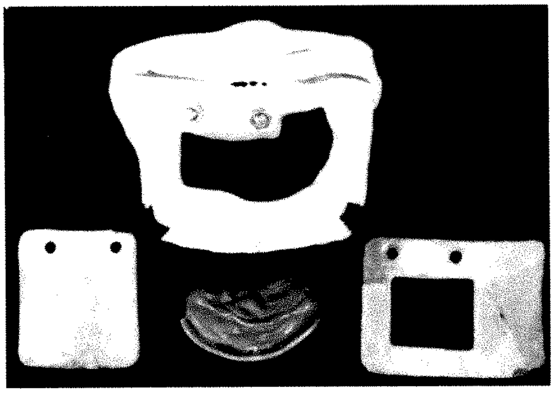

Fig. 14. Case ii. Mask, bite bar, and interchangeable field definers. The lesion for purpose of irradiation was divided into 3 areas: the patient's right area, mid area, and left area.

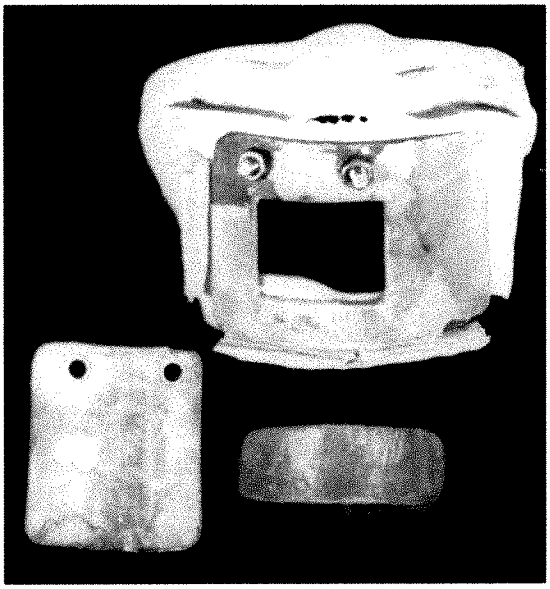

FIG. 15. Case II. Mask position for irradiation of right and mid areas.

September, the lesion had reduced to 8 sq. cm. The pin in the jaw was removed and 20 biopsies were made, all of which were negative (Fig. 20). A full thickness shift graft was done with 100 per cent take (Fig. 21). One year later, 2 small lymph node metastases were detected, both out of the radiation field, one in the parotid, the other in the inferior left neck. Both were proven by needle biopsy and both received full dosage radium needle implants. The patient is alive and well today (Fig. 22).

CASE IV. A 48 year old white male had a well differentiated squamous cell lesion of the right lip extending into the buccal mucosa, sulcus, and onto the lower alveolar ridge. A right external carotid catheter was inserted and from May 9, 1962 through May 29, 1962 he received 3,000 r in 15 treatments of 200 r each with a 20 cm. source skin distance cesium 137 unit. On May 29, 1962 the lesion was completely healed. No further therapy was given and he is alive and well at present.

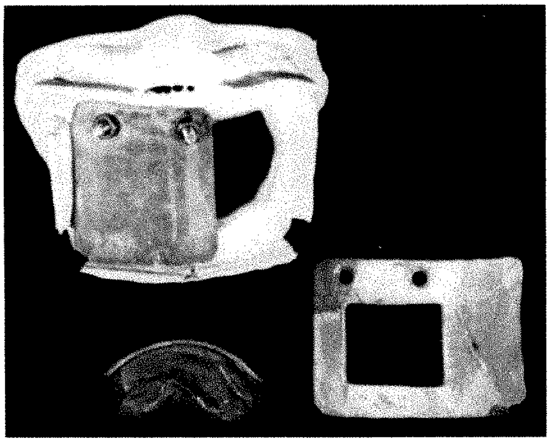

FIG. 16. Case II. Mask position for irradiation of left area.

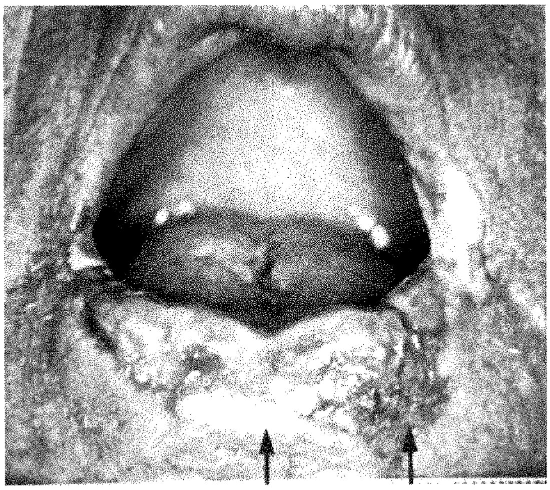

FIG. 17. Case II. After 3 weeks of therapy. Right and mid areas—3,000 r; left area—2,200 r. Note complete healing of left area.

CASE V. A 70 year old white female had a moderately differentiated squamous cell carcinoma of the left posterior oropharynx and hypopharynx, measuring 5×2×1 cm. with some necrosis. No enlarged cervical lymph nodes were felt. She showed a good distribution from a left external carotid catheter. She received 4,800 r in 16 treatments from July 24, 1962 through August 14, 1962, with the 2 mev.

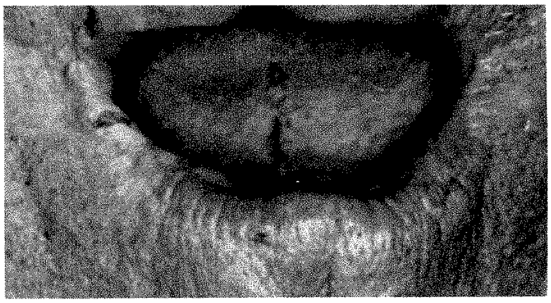

FIG. 18. Case II. Right and mid areas received an additional dose of 3,000 r, the total dose being 6,000 r in 6 weeks. Five months after completion of therapy the lip was totally healed.

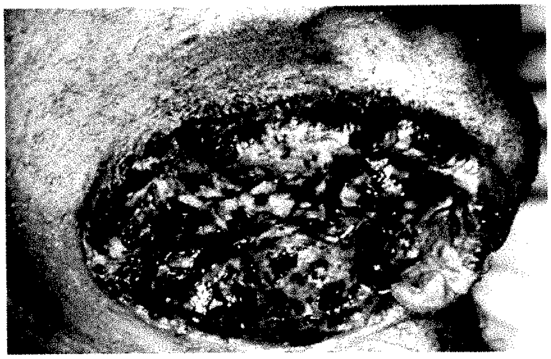

Fig. 19. Case III. Fungating metastatic carcinoma of the submental region from a squamous cell carcinoma of the lower lip and alveolar ridge, resected 2 years previously. Appearance before treatment. Note mandibular pin at 2 o'clock.

unit concurrent with infusion. At present she is alive and well.

Case VI. A 62 year old white female had a fibrosarcoma of the anterior part of the superior right turbinate of the nose. A right external carotid catheter showed excellent distribution of the infusion. She was treated with 2 mev. right angle wedge fields to include the right nose, antrum and anterior ethmoid cells, receiving 5,000 r in 15 treatments from December 5, 1962 through December 21, 1962. She is alive and well at present. She has minimal scarring of the right lacrimal duct with some watering of the right eye.

Case VII. A 16 year old white male had a firm mass protruding below the right costal cage. A radioactive rose bengal liver scan demonstrated a large defect in the liver consistent with this mass. Two doses of 250 r exposure each were given over the mass with the 2 mev. unit on April 11, 1962 and April 12, 1962. This is the approach we usually use in this institution.

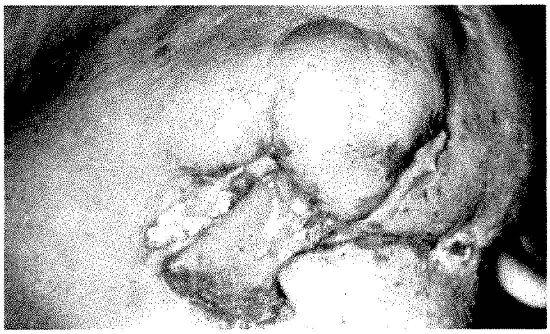

Fig. 20. Case III. Ten weeks following completion of therapy. The pin was recently removed. Biopsy study was negative. Note the appearance of the mandible.

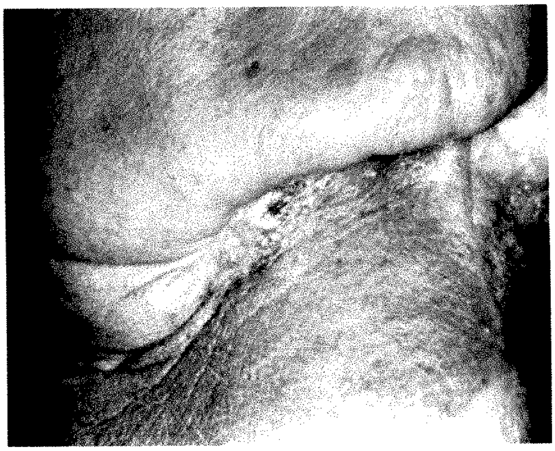

Fig. 21. Case III. Ten weeks following full thickness skin graft.

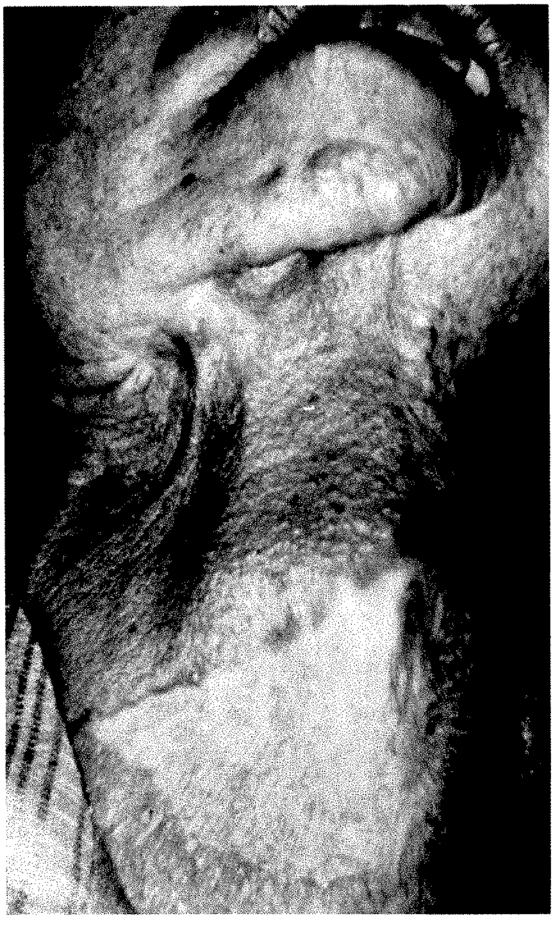

Fig. 22. Case III. Present appearance.

On April 13, 1962, the abdomen was opened, and after it was found that the mass involved all lobes of the liver, a biopsy was taken and it was closed. A catheter was placed through the femoral artery into the aorta in a retrograde fashion. The tip was localized just at the opening of the celiac axis. He received full liver irradiation with the 2 mev. unit concurrent with infusion. We delivered 3,500 r in 3 weeks (15 treatments) from April 22, 1963 through May 17, 1963. He is alive and well today, performing as a normal 17 year old boy. He has gained 20 pounds and his present liver scan shows marked improvement.

Case viii. A 64 year old white male was referred following an open biopsy of palpable left upper neck lymph nodes. The diagnosis was metastatic epidermoid carcinoma to lymph nodes. A 2 cm. carcinoma was found in the left posterior tongue at the base. The catheter was placed into the left external carotid artery via the superficial temporal artery. He received 5,250 r in 21 treatments from May 6, 1963 through June 4, 1963. He is alive and well today with minimal intermittent soft tissue swelling under the jaw.

FUTURE STUDIES

At the present time our techniques appear to be sufficiently stabilized to indicate that controlled studies should be attempted. It may be desirable to correlate tissue pO_2, tumor pO_2, infusion rate, and concentration, before proceeding with such studies provided this can be done in the near future. We are planning on this basis.

CONCLUSIONS

1. Regional oxygenation by the intra-arterial infusion of hydrogen peroxide is still an experimental procedure.
2. The results to date are sufficiently encouraging as to stimulate further studies of all the potential applications.
3. Preliminary results suggest an improvement in the therapeutic ratio utilizing this technique in conjunction with standard protracted radiation therapy.
4. No significant alteration of normal tissue radiation tolerance has been demonstrated using this technique to date.
5. It is probable that well controlled studies can be initiated in the near future, perhaps in a national cooperative type study.

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IRIDIUM 192 AS A RADIUM SUBSTITUTE*

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RADIUM has been in use for the treatment of cancer for more than 60 years; however, its limitations have evidenced themselves, and newer radioactive materials have been substituted in some of its areas in teletherapy, brachytherapy and interstitial therapy.

In teletherapy, the treatment of tumors with a beam of rays from radioactive material at a distance, radium has been replaced almost entirely by cobalt 60 and cesium 137. These artificial radioactive isotopes have a higher specific activity and source strength than radium. On the other hand, brachytherapy devices for intracavitary and mold treatments are still made with radium, since these are permanent, proved and unimproved upon by the newer isotopes. The prototype brachytherapy system is used for the treatment of cancer of the cervix, and, although attempts have been made to improve on radium for such treatments, nothing has, as yet, replaced its use in these cases. The Medical Division of the Oak Ridge Institute of Nuclear studies devoted several years of planning and research to develop more useful brachytherapy devices with artificial radioactive isotopes, but none has become universally adopted.

For interstitial implants of tumors, radium has distinct disadvantages. Radium needles are sometimes inaccurately placed because of their rigidity. The implant is adapted to the needle rather than the needle to the implant. The operator implanting radium needles must work quickly because of radiation exposure during the procedure. Along with this fear of radiation exposure while performing the implantation, is the concern of breaking a needle and spilling its content. These difficulties have dampened the radiotherapist's enthusiasm for the technique. Substitutes have therefore been developed to overcome the disadvantages in the use of the radium needles. Cobalt 60 is perhaps the most commonly used substitute. The design of the available cobalt 60 needles is essentially a copy of the tried and true radium needles. Since the radioactive cobalt does not have a potentially dangerous gaseous daughter element, it would appear to be superior to radium; however, cobalt 60 in needles has only minor advantage. Moreover, the annoyance of maintaining a bookkeeping account to calculate the decay of cobalt 60 is unnecessary with radium. Gold 198 in the form of seeds and tantalum 182 in hair-pin shape have their advocates, and appear to be useful in the hands of a select few. The purpose of the author is to point out some of the advantages of iridium 192 as a radium substitute.

ADVANTAGES OF IRIDIUM 192

1. EASY PROTECTION

Iridium 192 has a broad spectrum of gamma rays, like radium. The average energy of the iridium 192 gamma radiation is about 400 kv., considerably lower than the average of 1.2 mev. for radium. Insofar as protection is concerned, this is an appreciable advantage, since the half value layer in lead for iridium 192 is 3 mm. and 12 mm. for radium. The iridium 192 is commercially supplied in nylon tubing and prepared for use so that no hospital personnel is exposed to radiation before actual implantation in the operating room.

2. HIGH SPECIFIC ACTIVITY

The high cross section for neutrons of iridium makes it practical to supply a large

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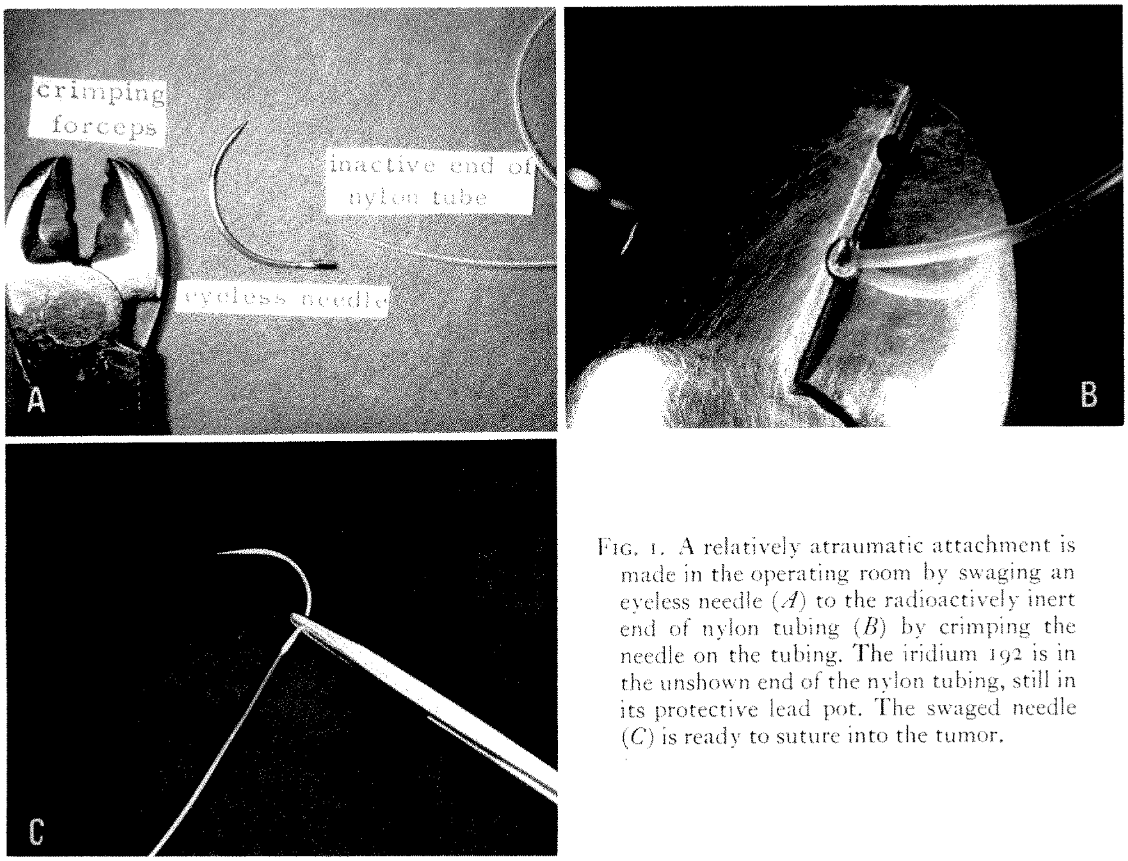

Fig. 1. A relatively atraumatic attachment is made in the operating room by swaging an eyeless needle (*A*) to the radioactively inert end of nylon tubing (*B*) by crimping the needle on the tubing. The iridium 192 is in the unshown end of the nylon tubing, still in its protective lead pot. The swaged needle (*C*) is ready to suture into the tumor.

range of activities of seeds. The seeds measure 0.5 mm.×3 mm. The commercial supplier furnishes the iridium 192 as milligram equivalents of radium. This allows the clinician to use familiar techniques for determination of dose in implants (*e.g.*, Paterson-Parker system), but it may introduce an inaccuracy due to the difference in quality.

3. FLEXIBILITY

The portion of the nylon tubing containing the iridium is within a protective lead pot, but each tube has a long radioactively inert end. The inactive end can be placed accurately in the tumor to the satisfaction of the operator without exposure to radiation. On completion of the implantation, the active ends of the tubing containing the iridium 192 are pulled into the implant and fixed there. It is only this final stage that is associated with radiation exposure to personnel in the operating room, and this stage can be done rapidly.

The inactive end of the nylon tubing may be inserted into the tumor in a way surgically most feasible. As an example, the tubing may be armed on a suturing needle, straight or curved, and actually sewn into the tumor. The radioactively inert end of the nylon tubing may be crimped on an eyeless needle (Fig. 1, *A*, *B* and *C*) to provide a relatively atraumatic suture. This may be done in the operating room when the proper needle can be selected. There is no radiation exposure during this procedure. If a smaller needle is needed, a short length of fine silk may be glued into the lumen of the inactive end of the nylon tubing (Fig. 2, *A* and *B*), and a less traumatic finer suture needle can be armed on the silk. In another method, hollow long straight needles can be inserted into a tumor and the nylon tubing can be inserted through the lumen of each needle. When the needles are withdrawn over the tubing, the tubing is in the geometric pattern established by the rigid needles.

Henschke *et al.*[1,2] have developed many of the devices for implantation of iridium 192 and have devised afterloading methods which promise to make the use of iridium 192 even more flexible. Liegner[4] has adapted these methods for the treatment of recurrent rectal carcinoma.

A significant problem in the use of iridium 192 is its expense ($75–150 per patient), if it is used just once. Henschke *et al.* have suggested techniques by which iridium 192 can be used over and over again.

METHOD AND MATERIAL

In an attempt to evaluate clinically the use of iridium 192 as a radium substitute in the implantation of tumors, 40 patients have been treated at the Mt. Sinai Hospital. The following selection of patients was made:

1. *Accessible and small tumors.* In patients with accessible and small tumors, usually the lesions are removed surgically, although some could be cured with radium. Our initial experiences have therefore been gained in a clinical evaluation of the response to iridium 192 implants in tumors which are not favorably treated by other methods. Small tumors have been treated in this series only when the patient had other lesions indicating a poor prognosis.

2. *Technical inoperability of patient.* Candidates for radical neck dissection because of metastatic carcinoma to the lymph nodes of the neck are, at times, technically inoperable on the basis of old age or intercurrent medical disease. In these instances iridium 192 implants may be indicated.

3. *Residual disease after resection.* Attempts to extirpate tumors radically by surgery are sometimes hindered by disease in an unresectable area. This could occur in the posterior region of a maxillectomy where tumor may be residual in the pterygoid fossa. Similarly, pelvic tumors may extend to involve the lateral pelvic wall and vessels. In these instances iridium 192 can be sutured into the sites containing residual tumor after resection.

4. *Palliation.* The most frequently treated case in our series is the patient with large fixed lymph nodes in the neck. Iridium 192 implants in this type of case are technically simple to perform, even with local anesthesia, and the implant is well tolerated by the patient. Usually, the radiotherapist hesitates to implant fixed neck masses because of the relatively simpler method of external irradiation. Also, he hesitates to make a large radium implant, because he and his personnel would receive too much radiation exposure for a palliative procedure. The lessened exposure with iridium 192 could extend the use of implants for palliation.

Examples of some of the 40 patients treated with iridium 192 in the Mt. Sinai Hospital are presented to show the technical aspects of these implants.

ILLUSTRATIVE CASES

CASE I. A small squamous cell carcinoma was found in the retromolar angle in a 60 year old woman who had recently recovered from an extensive operation for carcinoma of the bladder. Probability for long term survival was considered poor because of the extensive bladder tumor. The retromolar tumor extended to the floor of the mouth and measured 3 cm. in diameter (Fig. 2, *A* and *B*). Under local infiltration anesthesia, the lesion was implanted with iridium 192. Prior to implantation, a short length of silk was glued into the end of the nylon tubing to permit use of a fine curved needle to minimize trauma in the firm thin tissue overlying the mandible. The inactive end of the nylon tubing followed the silk. When the implantation was completed with all inactive tubing in place, these tubes were quickly drawn through the tumor, leaving the tubing containing the seeds of iridium 192 in the tumor. The tubing containing the seeds was fixed in place by crimping buttons on each side. The patient tolerated the implant well. The tumor received an estimated dose of 6,000 rads in 5 days. Subsequently, a neck dissection was done for a

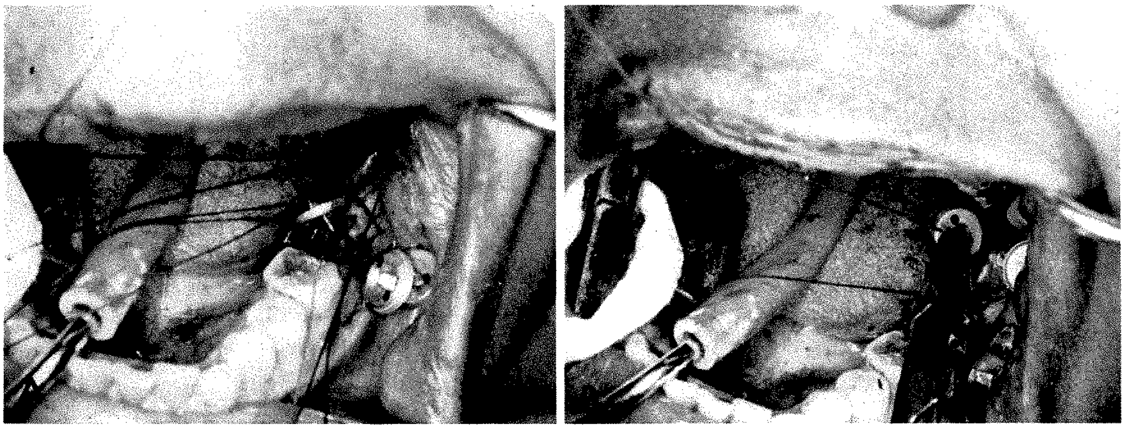

Fig. 2. Case i. The carcinoma in the left retromolar angle was not thick enough to allow suturing with ordinary needles, so thin silk (*A*) had been swaged on the radioactively inert end of nylon tubing to allow use of a thin needle. Then the section of tubing containing the iridium 192 was pulled through the tumor (*B*) and the implanted tubing was fixed in the tissue by crimping a metal button on each end.

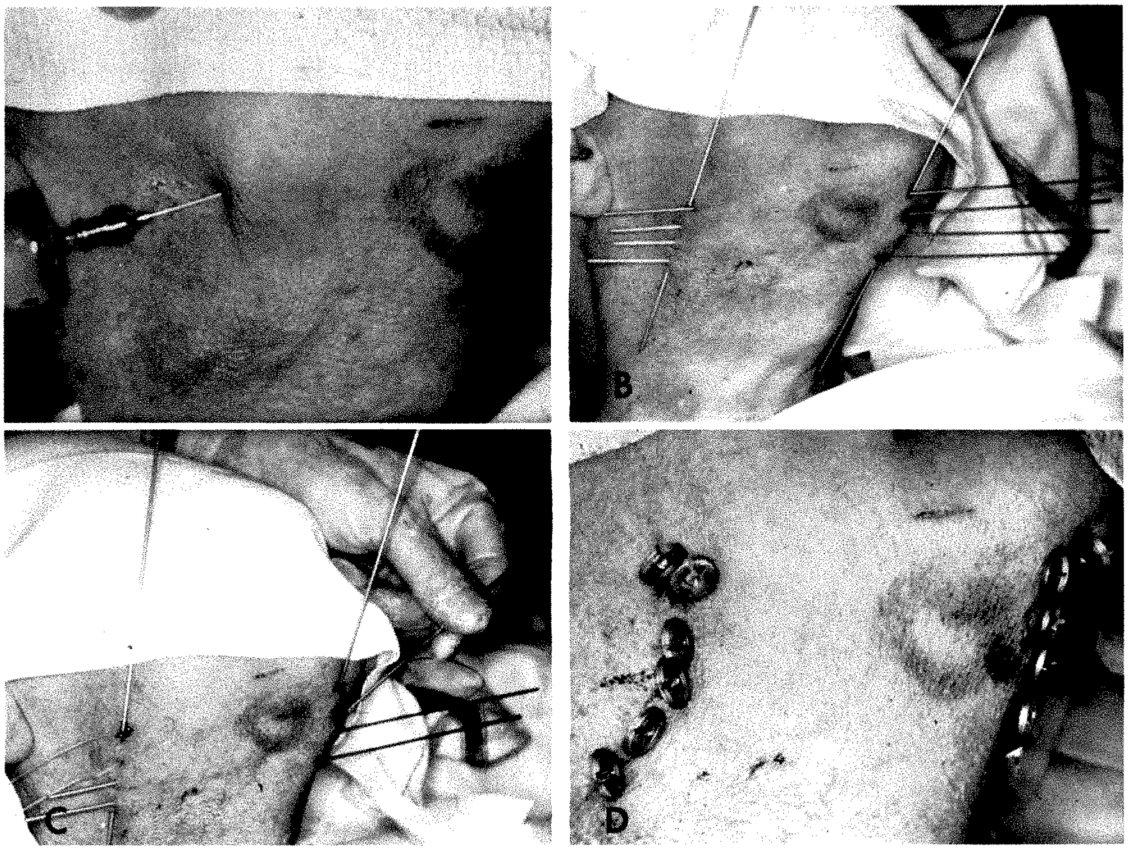

Fig. 3. Case ii. A metastatically involved right submaxillary lymph node, secondary to controlled squamous cell carcinoma of the tongue, was implanted under local (*A*) anesthesia. Hollow needles (*B*) were inserted in a geometrically satisfactory pattern. The radioactively inert ends of nylon tubing (*C*) were inserted into the needles, and the needles were withdrawn leaving the plastic tubing in place. When the iridium 192 seeds in the ends of the plastic tubing were drawn into the implant, they were fixed (*D*) by crimping metallic buttons.

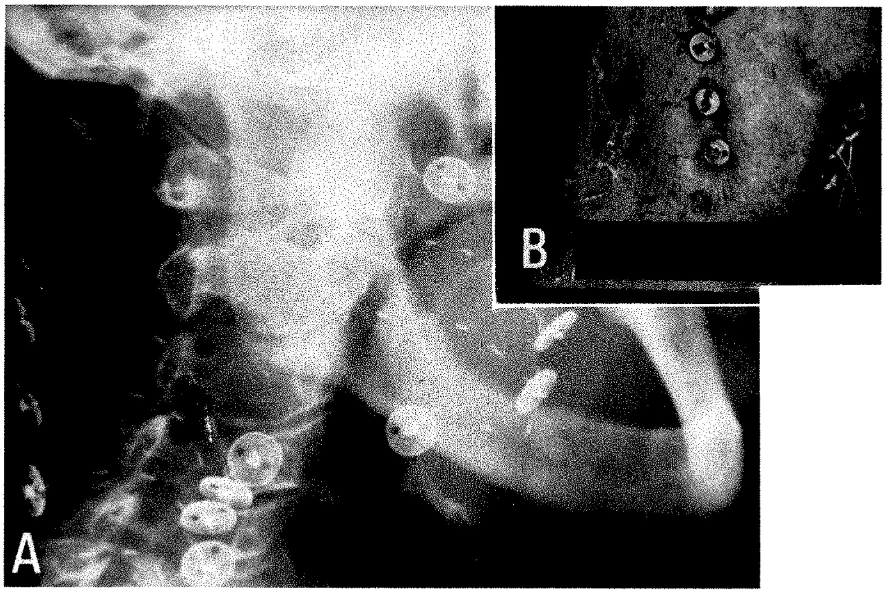

FIG. 4. Case v. Upper jugular lymph nodes were bilaterally involved by metastatic carcinoma from a primary tumor in the nasopharynx. There was not a complete response to external irradiation, and both sides of the neck were implanted with iridium 192. *A* shows the curvature of the implants corresponding to the curvature of the neck. There is no need for surgical dressing (*B*).

palpable mid-jugular lymph node, but this proved to be nonmalignant. Three years after this implantation, there is considerable telangiectasia, but no evidence of tumor at the site of irradiation. This lesion could have been resected surgically, but it would have been a difficult tumor to implant with radon seeds and practically impossible to implant with radium needles. The location required the flexibility which the iridium 192 in nylon tubing provided.

CASE II. A metastatic lymph node in the left submaxillary region was considered technically inoperable in an 85 year old man who had previously had a radium implant of a carcinoma of the tongue with local control of his tumor. Under local anesthesia a geometrically ideal planar implant was made with hollow trochars (Fig. 3, *A–D*). These were used as guides for the placement of the radioactive material. The iridium 192 remained in place comfortably for 1

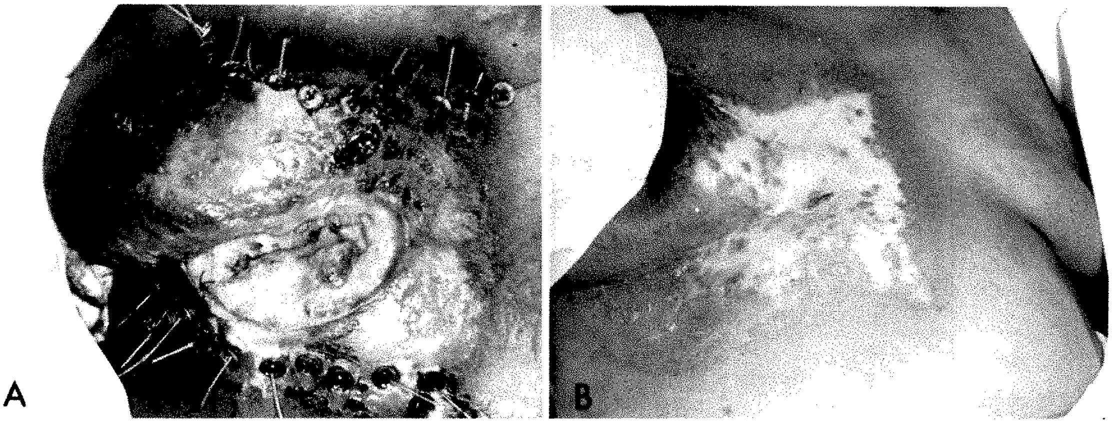

FIG. 5. Case VI. A large fungating scirrhous carcinoma of the medial half of the right breast failed to respond completely to electron beam therapy. An implantation with iridium 192 was made. The implant (*A*) measured 15×15 cm. and remained in place for 1 week delivering a dose of 3,500 rads. Ten months later (*B*) there was only an ulceration in the center of the former and marked depigmentation of the skin.

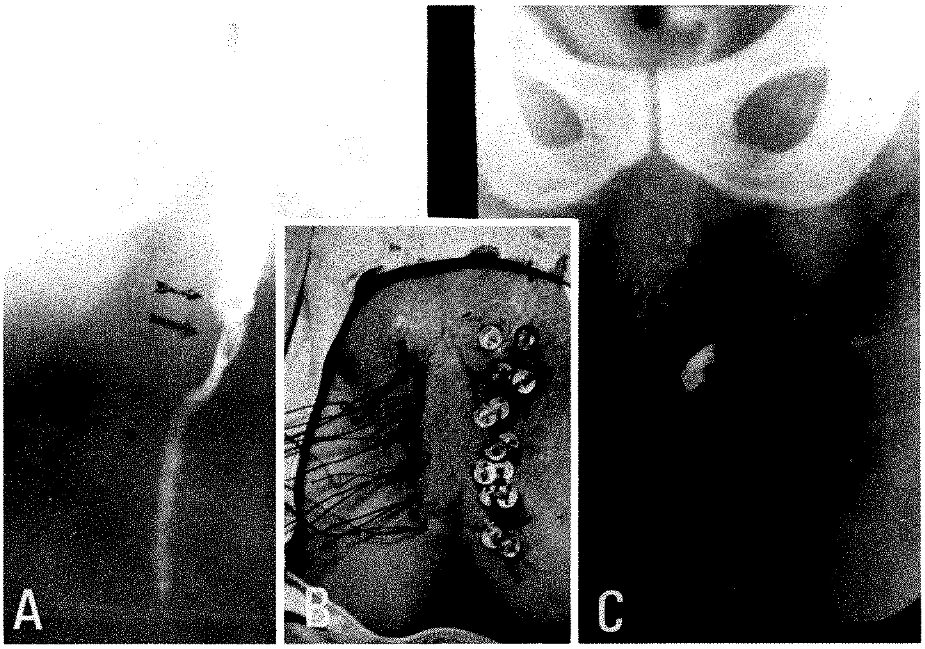

Fig. 6. Case vii. An unusual carcinoma of the perineal urethra in an elderly man appeared as nodular defects in a urethrogram (*A*). Loops of nylon tubing were placed so as to encircle the tumor (*C*), and the loops were fixed in the perineum by crimping buttons (*B*).

week for a dose of 5,000 rads, and the subsequent radiation reaction was appropriate and tolerable. The patient is surviving 3 years later without evidence of tumor.

Case iii. A 60 year old woman had a teratocarcinoma of the uterus removed surgically, but 1 year later it recurred as a 3 cm. mass in the vault of the vagina. This mass was implanted with radium needles, and appeared to be controlled. Six months later, a mass in the left pelvis was subtotally removed at laparotomy. Residual tumor was fixed to the left pelvic wall with the iliac vessels and the left ureter enveloped by the mass, which could not be removed without sacrifice of the pelvic wall structures. An implant of iridium 192 was sewn into the left lateral pelvic wall through the residual tumor. The inactive ends of the nylon tubing came out of the abdominal wall along with the surgical drains. After an estimated dose of 6,000 rads to the left pelvic wall, the iridium 192 implant was removed, and the drains were shortened. The only unusual features of this case were rather slow healing and long drainage of the pelvic wound. Eight months after operation there is no palpable evidence of disease, and the patient is well.

Case iv. An 80 year old man with carcinoma of the right antrum had a maxillectomy, but the posterior wall of the antrum still contained a small deposit of tumor which could not be removed with an adequate margin of normal tissue. Nylon tubing was sutured into the floor of the antrum and maintained in place by the packing used to fill the defect. The operative defect was lined by a large skin graft, and the nylon tubing containing the iridium 192 seeds lay directly under the skin graft. After a dose of 4,000 rads, the tubing was removed with care to prevent disturbing the skin graft lining the defect, and healing was uneventful.

Case v. Most of the treatments in our series were palliative. The most commonly treated lesion of this palliative type is exemplified by the 60 year old man whose primary squamous cell carcinoma of the nasopharynx was controlled, but external irradiation failed to cure the bilateral upper jugular metastatic lymph nodes fixed to the underlying bone. Bilateral iridium 192 implantation of these lymph nodes (Fig. 4, *A* and *B*) was made with the technique of inserting hollow needles and subsequently pulling the active nylon tubing into the needles. The procedure was tolerated well, the patient

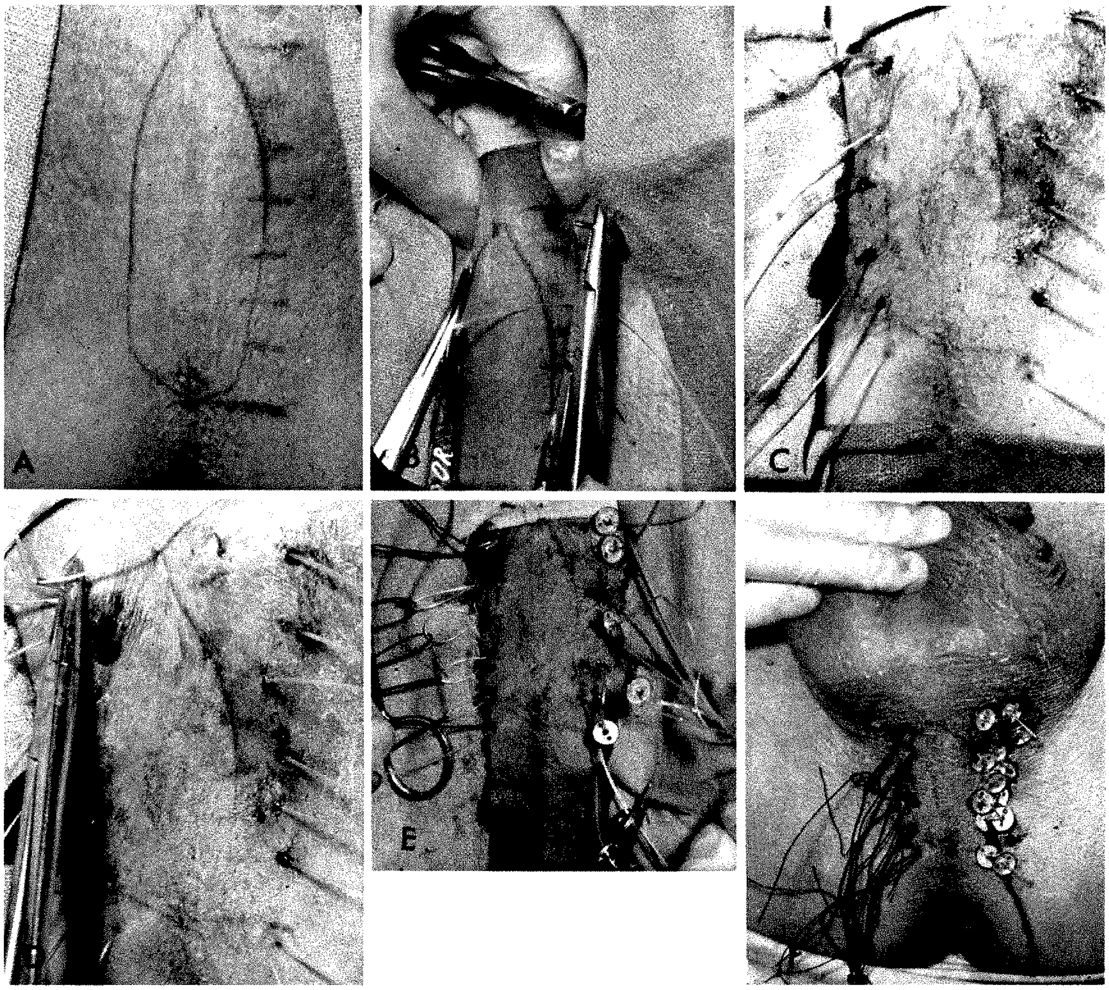

Fig. 7. Case vii. The perineum was marked with dye (*A*) to indicate the cylinder of the urethra and tumor to be implanted. Large curved needles were placed deep to the tumor (*B*) and the nylon tubing was threaded deep to the urethra in an array of arches (*C*). Then the same needles were entered into the skin back through the holes from which they emerged, but this time the needles were pushed through subcutaneously, superficial to the tumor and urethra (*D*). Complete loops of nylon tubing are seen surrounding the tumor at 1 cm. intervals (*E*). When the active ends of the tubings were drawn through the implant and fixed on the skin with metallic buttons (*F*), the tumor lay in a cylinder of radioactivity. The thick silk sutures seen on the left are used for traction on the embedded loops to simplify removal of the implant.

being able to move his neck freely even while the implants in the upper half of both sides of the neck were in place. The patient has survived for 2 years. Similar implantations have been made in other instances, and the tolerance of the patients and the ease of making these implanations have been most impressive.

Case vi. Palliative implantations may include another broad category of patients with extremely large tumors which the radiotherapist would hesitate to implant because of the large amount of radiation exposure to personnel. As an example, this 50 year old woman had a large tumor occupying the entire right breast (Fig. 5, *A* and *B*). Hollow needles were inserted and an accurate distribution of iridium 192 was obtained. Operating personnel received a dose of less than 20 mr. This low dose to the surgeons was attributable to the technique described with iridium 192 and also to the convenience of obtaining iridium 192 at any desired activity. In this case, an activity of 0.2 mg. of radium equivalent per seed was used, and the implant was allowed to remain in place for a correspond-

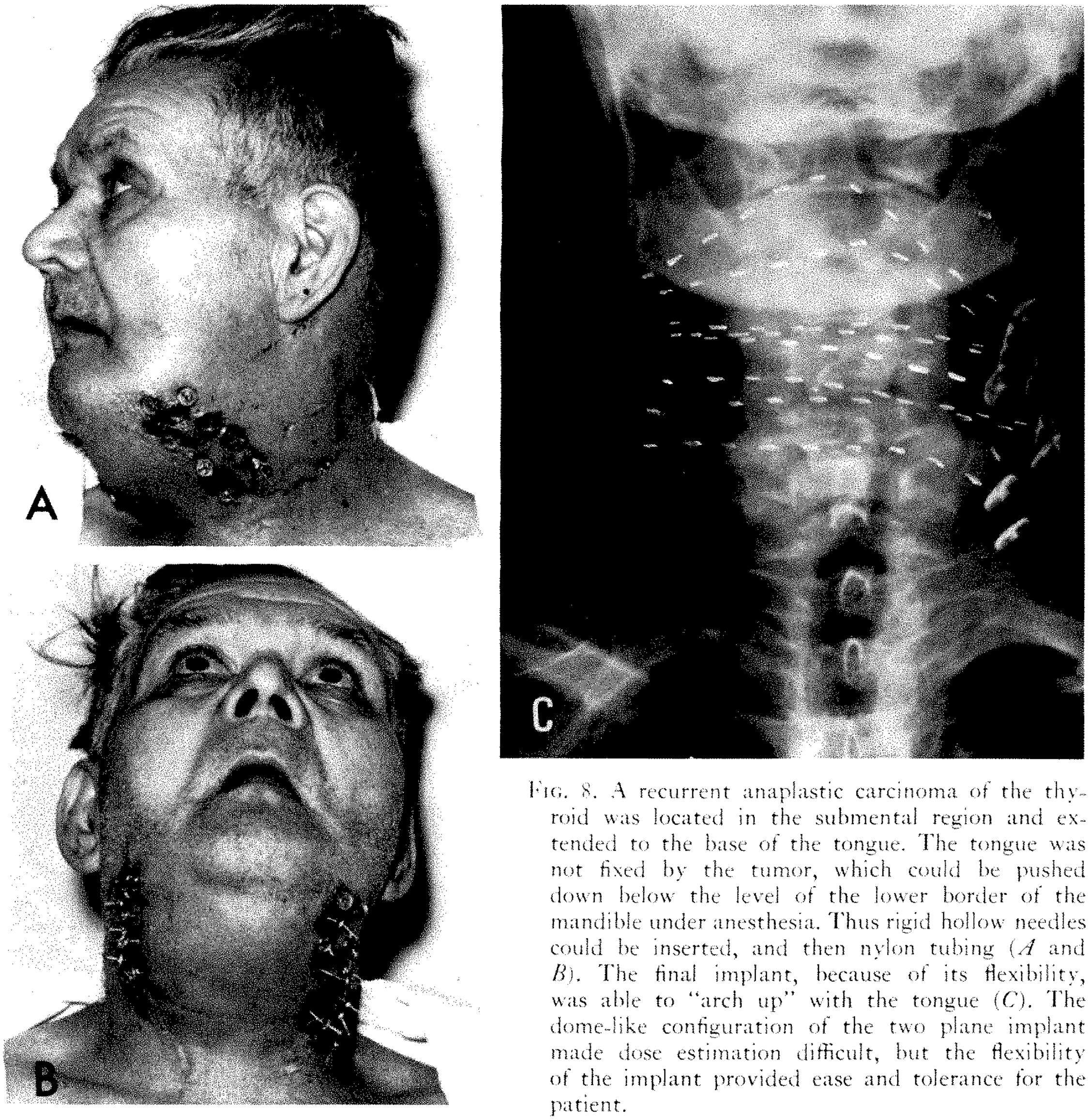

Fig. 8. A recurrent anaplastic carcinoma of the thyroid was located in the submental region and extended to the base of the tongue. The tongue was not fixed by the tumor, which could be pushed down below the level of the lower border of the mandible under anesthesia. Thus rigid hollow needles could be inserted, and then nylon tubing (*A* and *B*). The final implant, because of its flexibility, was able to "arch up" with the tongue (*C*). The dome-like configuration of the two plane implant made dose estimation difficult, but the flexibility of the implant provided ease and tolerance for the patient.

ingly longer time. The right anterior chest wall received a dose of 3,500 rads in 1 week; the breast cancer was previously treated with the electron beam. This residual tumor required an iridium 192 implant measuring 15×15 cm. All sources in the implant were of equal strength, so the homogeneity of dose in the implant plane was improved by removing the inner sources of iridium before the periphery. In effect, this procedure simulated differential loading.

Case vii. The flexibility and patient tolerance of iridium 192 implants were demonstrated in the treatment of a 75 year old man with a painful carcinoma of the perineal urethra. The squamous cell carcinoma was palpable through the overlying skin of the perineum as a firm cylinder, 2 cm. in diameter and 5 cm. in length. The patient was considered technically inoperable. He had had two previous coronary occlusions, and he was on anticoagulant therapy. An iridium 192 implant was placed so as to surround the tumor (Fig. 6, *A*, *B* and *C*; and 7, *A*-*F*). The procedure was done under general anesthesia, using an indwelling catheter during the operation and postoperatively. A series of loops of nylon tubing containing iridium 192 was placed so as to encircle the tumor, making an accurately placed cylinder around the cylindrical tumor. After a dose of 5,000 rads in one week, the implant and catheter were removed. The implant and the radiation reaction were well tolerated. The pain in the perineum subsided; however, 4 months later the patient died. Death was caused by cerebral disease, either vascular or metastatic, but relief of urinary symptoms justified the implantation procedure.

DOSIMETRY

The problems of dosimetry are not completely solved. Iridium 192 is provided commercially in milligrams of radium equivalents. This enables the radiotherapist to estimate doses simply, satisfying the rules of Paterson and Parker. However, there are factors which make this dosimetric analysis less than ideal. The average energy of the gamma rays of iridium 192 (400 kv.) is considerably less than that of radium (1.2 mev.). Clinically, the reactions seem to be "hotter" than would be expected with a radium implant. This was particularly apparent in one patient whose lower neck was implanted with iridium 192 to a dose of 5,000 rads (minimum), but the skin response appeared to be what might be expected with as much as 7,000 rads.

Another dosimetric problem arises from the very versatility of the iridium 192 implant material. At times, tumors of irregular shape can be implanted in distributions not technically possible with radium (Fig. 6, *A–C*; 7, *A–F*; and 8, *A–C*). As a result, none of the previously determined dosage schemes for known geometric patterns satisfies the specific situation. Compromises have to be made until such time as methods of direct measurement are sufficiently advanced and available. A step in the proper direction is represented by the work of Laughlin *et al.*[3] on computer analysis of implants, but even these require prior data on the geometric distribution. Direct measurement of the skin or mucosal surface with scintillation crystals is of potential importance, but it is unusual for a measurement of the skin or surface to be of clinical value.

SUMMARY

Iridium 192 represents an appreciable advance and advantage over radium for implantation of tumors. Its flexibility expands the indications for implants, for the radioactive material is in plastic tubing which can be sewn into accessible lesions. Accuracy of placement of the iridium 192 is superior to radium, for the implants are made with radioactively inert ends of the implant material. Along with increase of accuracy, there is less radiation exposure to the radiotherapist.

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A NOTE ON THE DOSIMETRY OF TANTALUM 182 WIRES*

By KALEVI KETTUNEN, M.D., P. I. TUOVINEN, M.D., *and* E. VAURAMO, B.A.
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INADEQUACIES of dosimetry have limited the utilization of radioactive tantalum wires in radiation therapy of bladder carcinoma. At the present two methods—the point dose calculation and the isodose calculation method—are in use. In the former method, the dose is measured at a single point, and the length of the treatment time is determined on the basis of the value obtained in this manner. Attention has, however, been drawn to the fact that the dose distribution is nonhomogeneous, so that the estimate obtained by means of a single point is erroneous and may be misleading. In the latter method, again the determination of isodoses from the diffuse three-dimensional figure formed by the tantalum wires in the walls of the bladder is a laborious and difficult task. Moreover, in the majority of cases the result is of little value, for the dose for a particular area is in itself no biologic expression.

When an attempt is made to find an adequate solution, the fact that necrosis of the tumor produced by a certain amount of radiation is the only biologically meaningful characteristic should be taken as the point of departure. Necrosis, in turn, is a function of time, dose, the quality of the tissue and the irradiation geometry.

As regards the time-dose relation of the tumor, we have chosen Paterson's[1] studies as our guide. According to these, the tumor lethal dose for epidermoid carcinoma is, on the average, as follows: 1 day—2,000 r; 4 days—4,000 r; 8 days—5,000 r; 12 days—5,500 r; and 32 days—6,000 r.

Of course, the quality of the tissues, in other words their radiosensitivity, affects

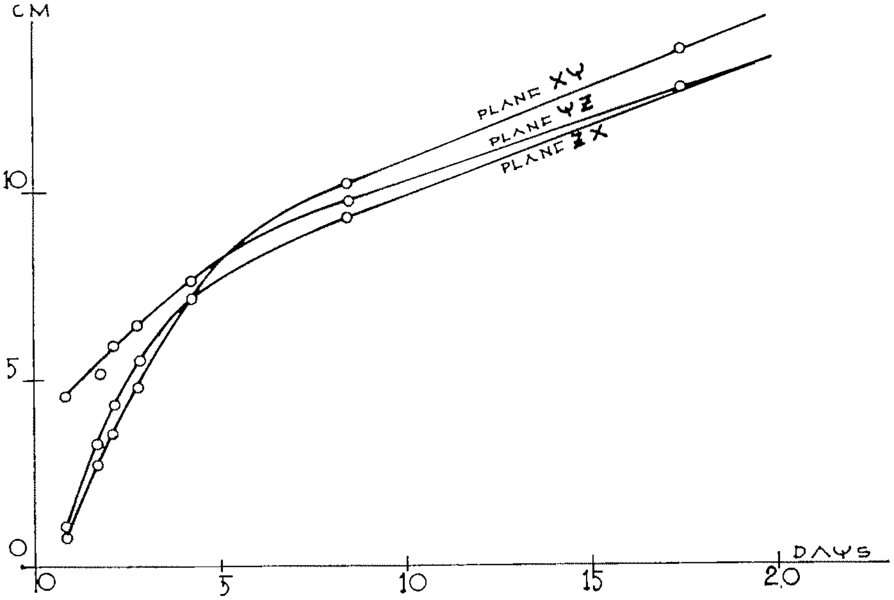

Fig. 1. Dynamic model dosimetry. Comparison between different planes. The curves represent the diameter of that circle in different planes that a 2,000 r dose forms in a 1 tantalum 182 wire system as a function of time.

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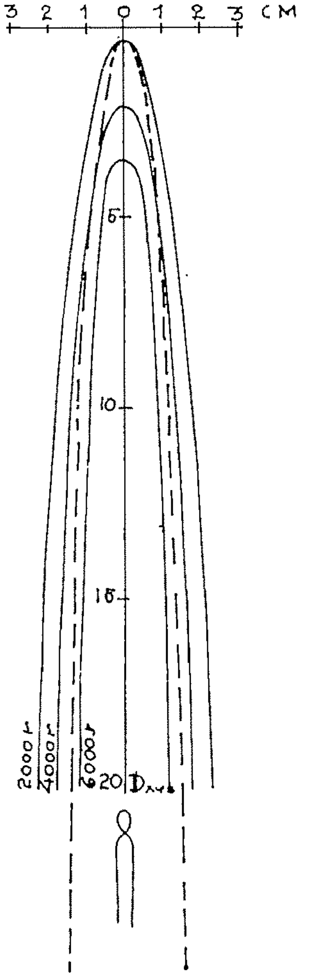

Fig. 2. Typical dynamic model dosimetry curves for a 1 tantalum 182 wire system, where the diameter of the circle has been drawn as a function of time for standard doses. The broken line indicates the tumor lethal dose, according to Paterson, as a function of time.

the amount of necrosis to some extent, the effective factor being mainly the oxygen content of the tumor. For the present, no such biologic information is available about this that could be directly connected with dosimetry. Therefore, we have disregraded the difference between tissues, especially since this factor is of minor significance due to the fact that tantalum wires are, as a rule, implanted in the tumor tissue and used for local treatment.

Radiation geometry constitutes a problem which is difficult to solve. In the Maria Hospital, the tumor dose was calculated first employing certain predetermined geometric forms. Roentgenographic determination of the location of the wires revealed, however, that none of the predetermined forms had been obtained; hence, the method was abandoned. During the period when use was made of isodose calculation, the geometry became quite important. It was discovered that, when the wires intersected one another in a certain manner, the dose in an area within the tumor might be 10 times the peripheral dose. This meant that in cases where the periphery of the tumor was exposed to 2,000 r, the dose in its center might amount to 20,000 r. Not

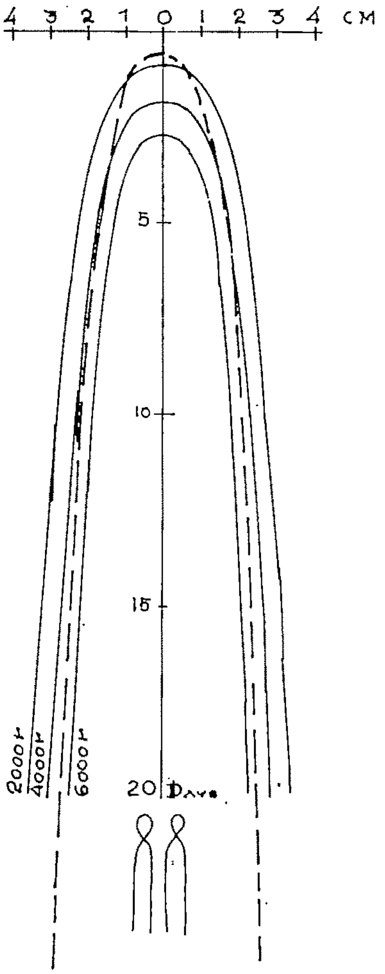

Fig. 3. Dynamic model dosimetry curves for a 2 parallel tantalum 182 wire system.

much biologic significance, however, is attached to this circumstance, inasmuch as at such a point the tissue has already necrosed. On the other hand, it is important to determine the peripheral tumor dose because the central dose is always high enough if the peripheral part of tumor has received a lethal dose.

For this reason, we use at the Maria Hospital a dynamic model of dosimetry. The propagation velocity of necrosis from the center of the radiation field as a function of time-dose relationship, based on Paterson's studies, is employed. We have computed several typical curves for it.

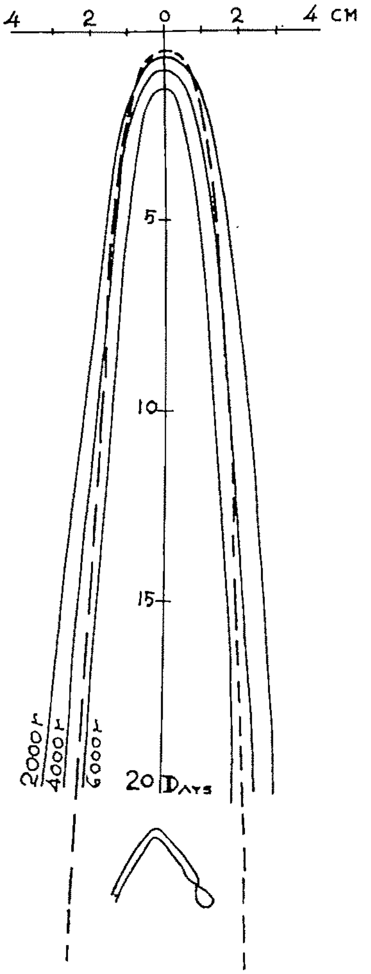

Fig. 4. Dynamic model dosimetry curves for a 1 angulated tantalum 182 wire system.

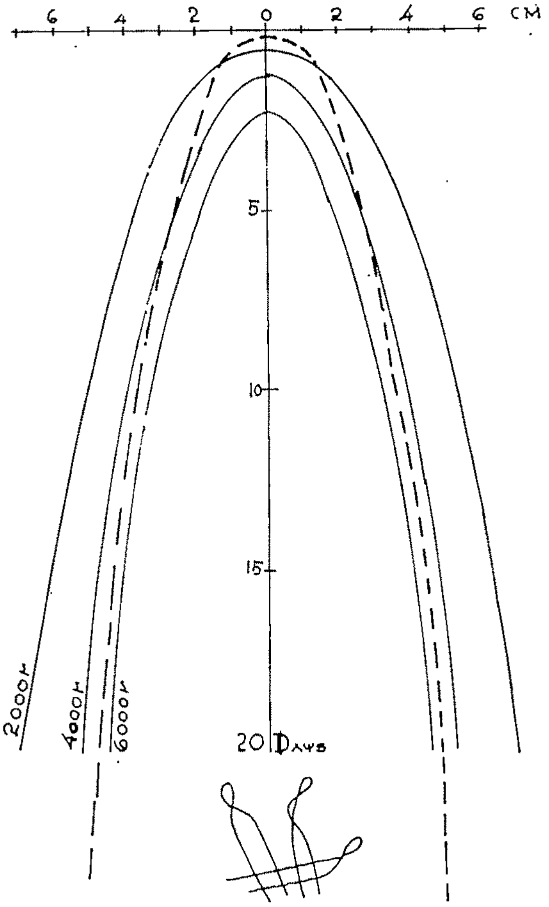

Fig. 5. Dynamic model dosimetry curves for a 3 tantalum 182 wire system.

The curves have been calculated for wires of the hairpin type whose activity is of the order of 12.5 mc apiece (Amersham Type TAW 8 Type "C"). The principle underlying the dynamic model dosimetry is that it is independent of the radioactive element used and correction for half-life is easily accomplished. In practice, the distribution is always space-symmetric to a sufficient degree of accuracy. A space-geometric analysis of a typical case is shown in Figure 1. From this figure it is apparent that the irregularity in the 2,000 r curve, due to geometry, gradually disappears as the distance from the center of the tumor increases. Dosage differences in the center are of little importance because necrosis will occur at the center in any case.

Figures 2 to 5 reveal the surprising feature that the effect of irradiation occurs chiefly in the first days. The later days are of little significance. Figures 2 and 4, for example, show that when 1 wire is employed, the necrosed area in 1 day is 10 to 13 mm. in diameter. In 5 more days the diameter of the necrosing area has only increased to 14–20 mm. Figure 5 illustrates that, in a system of 3 wires, the necrosing area obtained in the first day is 30 mm. in diameter; after 5 days it measures 50 mm. In systems of 1 and 2 wires, the progression of the edge of the necrosing area comes practically to a standstill within 5 days, and its diameter is doubled only after weeks. Considerable retardation also takes place in 3 wire systems; after the first day the diameter increases by 1 cm. every 2½ days.

Considering that the increase in the diameter of the necrosing area is about 2 to 3 mm. per day when small wire systems are employed and about 0.5 cm. per day when use is made of larger wire systems, it is apparent that an exact determination of the irradiation time and dose is not biologically meaningful, for the edge of the tumor cannot be determined to any high degree of accuracy; it can be determined with an accuracy of 0.5 cm. at best. This indicates that it is sufficient to determine the length of the treatment period based on the 1 day effect, the dose in terms of roentgen being subject to an error of 20 to 30 per cent. No significance in this analysis is attributed to the roentgen dose as such, for the absolute dose is not a clinically meaningful magnitude, except in conjunction with the length of the treatment time.

SUMMARY

An attempt is made to demonstrate that accurate physical dosimetry does not in itself yield a biologically meaningful result. Moreover, we have dispensed with the use of the roentgen unit and replaced it by a biologic characteristic, *viz.*, the progression of the necrosing area as a function of time-dose relationship. This procedure has been adopted in the Maria Hospital when tantalum 182 wires are employed for radiation therapy.

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A COMPACT RADIUM SAFE EMPLOYING GAS STERILIZATION*

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IN MANY existing designs of radium safes, the radium sources are housed in massive lead blocks which are not easily removable from the safe, so that sources must be removed from the safe one at a time. In some designs the protection of personnel in front of the safe depends on a massively-shielded door, and repeated access to the safe for removal of sources may, therefore, involve exposures to high radiation dose rates. The handling of radium needles prior to interstitial use presents further problems. After removal from the safe, needles must be threaded, if this has not been done before storage, and subsequently they must be sterilized and transported to an operating room. Frequently, the radiation protection during sterilization and transportation is of a casual nature. Moreover, these procedures, in our experience, frequently lead to entanglement of the threads with consequent time delay and unnecessary radiation exposure of personnel.

A plan for radium needle handling starts at the safe and ends with return to the safe. In working out such a plan, we have evolved a new design for a radium safe and a scheme for threading, sterilization, transportation and record keeping. The safe described here is primarily intended for threaded needles, but may also be used for short radium tubes. Other devices for radium tube storage have been described, which dispense selected single sources for use in applicators or moulages. Safes of this kind are commercially available. A novel dispenser of this kind has been designed by Braestrup.[2]

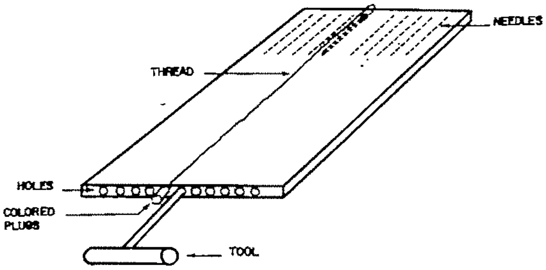

FIG. 1. Sketch of stainless steel plate for holding threaded radium needles.

THE DESIGN CONCEPT

One method of storing threaded radium needles is to insert them into a metal plate and wrap the threads individually around the plate, finally securing them. Several needles, preferably of a similar kind, may be stored per plate. To provide maximal protection to the hands when transporting the plate, the needles may be carried in one end of a long plate, and a handling tool inserted into the other end. This concept is shown in Figure 1.

The use of metal plates permits their integration into a small highly protected metal block for their storage. A highly efficient safe results from the concept of a solid metal cuboid block at the remote side of which radium sources are housed, but which permits access to the sources from the front, highly-protected face. Such a block may consist of a stack of plates, each of which serves as a needle carrier and also as part of the protective slab. As shown in Figure 2, this array of plates would require further stationary protection around the rear portion.

The feasibility of this idea depends on

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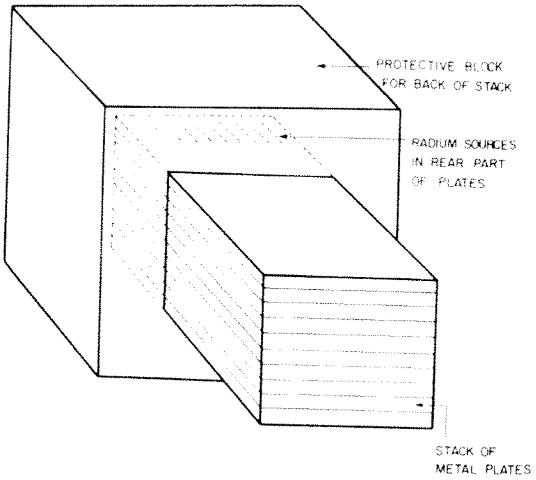
PROTECTIVE BLOCK FOR BACK OF STACK
RADIUM SOURCES IN REAR PART OF PLATES
STACK OF METAL PLATES

FIG. 2. Concept of safe for storage of small radioactive sources.

the size of the plates required for adequate protection. The thickness of steel necessary for 500 mg. of radium and yielding, for example, 50 mr/hr. at the front of the array is 6 to 8 inches, depending on the radium distribution. The plates should be light, *i.e.*, 1 to 2 pounds, so that they may be easily manipulated at the end of a handling tool.

DESIGN DETAILS

To reduce the weight of each plate and to permit adequate subdivision and distribution of the total amount of radium to be stored, the "metal block" is divided into two tiers each with 10 plates. Each plate is 7 inches long, 3 inches wide and $\frac{1}{4}$ inch thick with a finished weight of about 18 ounces. The safe proper, including the outside container for supporting the plates, is only 7 inches wide, $3\frac{1}{2}$ inches high and 8 inches deep (Fig. 3). Stainless steel was chosen because of its noncorrosive properties and because it is easily decontaminated.

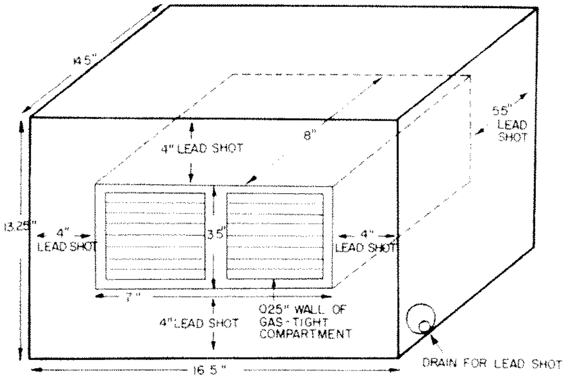

FIG. 3. Dimensions and protection for radium safe.

Each plate is drilled axially at one end with 10 equally spaced holes. All the holes in any one plate are of the same depth. Depths are chosen to accommodate needles of different lengths up to 6 cm. (Fig. 4). Each hole is counterbored $\frac{1}{2}$ inch deep to $\frac{3}{16}$ inch diameter to accept a closing plug. The thread (double nylon) from each needle is carried back tautly over the surface of the plate and is fastened in the front hole by a colored plastic plug (Fig. 1). This arrangement maintains the needles in the bottom of the plates when held vertically.

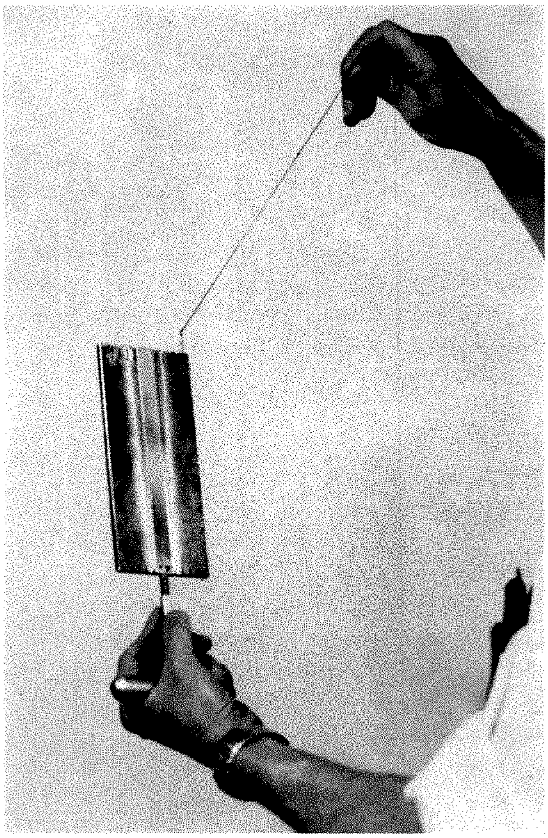

FIG. 4. Removal of threaded radium needle from steel carrying plate.

The principal protection problem in this design is the dose rate at the access side of the safe. In order to avoid a heavy lead door and to protect the hands during plate withdrawal, the steel plates must be adequately long and closely-fitting. For guidance regarding maximum permissible dose-rates around the closed safe, particularly at the access face, we referred to three standards:

1. The classification of a room as a "radiation area," rather than a "high radiation area," due to the presence of the safe. The Code of Federal Regulations, Title 10, Chapter 20, requires that the exposure-rate at 1 foot from the safe should not exceed 100 mr/hr. This leads to a thickness of 4 inches of steel for a concentrated source of 500 mg.
2. The I.C.C. Shipping Regulations for radioactive materials specify an exposure rate not greater than 200 mr/hr. at the surface of a container and not greater than 10 mr/hr. at 1 meter. The latter condition suggests a minimum steel thickness of 5 inches for 500 mg.; while for distributed sources, the surface dose condition also requires about 5 inches of steel.
3. The maximum permissible exposure rate at 1 meter from teletherapy sources is also 10 mr/hr. (NBS Handbook 73).

In our design the thickness of steel from the center of the radium sources varies between 5¼ and 6 inches. The safe, however, is not a solid block of steel. There must be clearance between the steel plates to allow for easy withdrawal, and more importantly to accommodate the threads attached to the needles. Through these gaps, narrow beams of higher dose rate will emerge. Since the area of these gaps is small compared with the over-all area occupied by solid steel, a factor of 2 to 4 times higher dose rate is considered to be acceptable at these gaps. This would not unduly affect the average radiation dose rate at the front of the safe.

On the basis of plates ¼ inch thick, the maximum size of clearance permissible between the plates may be calculated. One approximate approach is to consider that the presence of the gaps reduces the average density of the steel. The half value layer of well-filtered Ra gamma rays in steel is about ¾ inch. Hence the reduction of effective steel thickness from 6 to 5¼ inches will approximately double the average surface exposure rate. The air gap b per plate which will reduce the over-all density in the ratio 6 to 5¼ is given by the relation:

$$\frac{6}{5\frac{1}{4}} = \frac{b + 1/4}{1/4},$$

whence $b = 1/28$ inch.

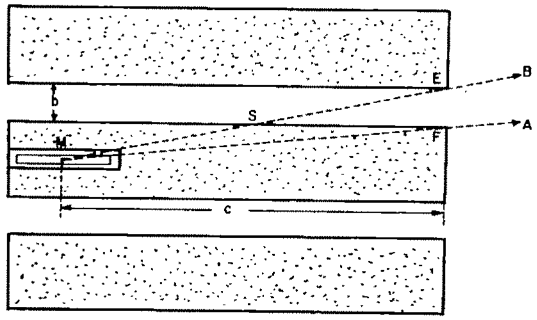

Fig. 5. Leakage of gamma rays through gaps between plates.

The exposure rate at the leakage gaps depends strongly on the clearance between the plates. Referring to Figure 5, the difference in the thickness of steel traversed by ray A passing through the plate entirely and ray B which passes largely through the air gap is given by:

$$\mathrm{MF} - \mathrm{MS} = \mathrm{SE} = c\left[\frac{2b}{2b + a}\right].$$

For $c = 6$ inches and $a = \frac{1}{4}$ inch, this difference equals 1 half value layer (¾ inch) when $b = 1/56$ inch, and equals 2 half value layers (1½ inches) when $b = 1/24$ inch. It is obvious that the clearance must be kept as small as possible and not greater than 1/24 inch if the steel protection is not to be seriously impaired.

The determining factor regarding the clearance is the thickness of the nylon thread used for the needles; 0.25 mm. thread is normally used in double thickness. In order to accommodate a length of double

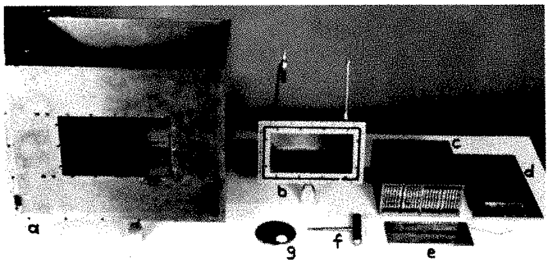

FIG. 6. Components of radium safe: (a) outer brass container, (b) inner gas-tight box showing gas fittings and gasket for door, (c) stainless steel safe compartment with 19 steel plates, (d) door with $\frac{1}{2}$ inch lead liner, (e) steel plate, (f) spring-loaded tool for handling plates, (g) cover for lead-shot drain.

thread of at least 12 inches, it is necessary to accommodate 2 runs of double thread over the top of the plate from each needle. Therefore, it is possible to have up to 4 thicknesses of thread stacked between the plates. This would suggest a clearance of 1 mm. or 1/25 inch above each plate. In practice we have found that a clearance of 1/32 inch gives an easy push fit to the plates without cutting or damaging the threads. This clearance is permissible from a protection standpoint.

EXTERNAL LEAD PROTECTION

Although only the rear portion of the steel block is required to be encased in lead, actually all sides except the front side are so protected. The steel provides considerable lateral protection so that on the sides only 3 inch thickness of lead is employed. At the rear the lead thickness is increased to 3.75 inches. Whether or not this is necessary depends on the wall structure behind the safe and the occupancy of the area beyond. The small door to the safe contains a thickness of only $\frac{1}{2}$ inch lead.

For ease in adding this protection, lead shot #4 gauge (approximately $\frac{1}{8}$ inch diameter) was used. The measured density of this material was 7.68 g./cm.^{3}, or a little more than $\frac{2}{3}$ the density of cast lead. Therefore, the above lead spaces have been increased 50 per cent to $4\frac{1}{2}$ and $5\frac{1}{2}$ inches, respectively (Fig. 3). The entire safe ensemble is shown in Figure 6.

STERILIZATION OF RADIUM SOURCES

Reported methods of sterilizing radium sources involve either immersing them in boiling water[3] or in a liquid such as benzalkonium chloride (zephiran).[7] Boiling of radium sources has resulted in at least one serious accident,[4] involving the explosive rupture of the source. Morgan[8] has shown that the gas pressure within a radium capsule can build up considerably with time, following the sealing of the radium in the capsule. Liquid sterilization by a nontoxic sterilant is preferable. However, it has been shown that zephiran may not be an effective sterilant[5,6,10] since there have been cases of infection resulting from the use of catheters and instruments after immersion in zephiran. The results of our own investigations[1] are consistent with these findings.

In 1949, Phillips and Kaye[9] reported on "The sterilizing action of gaseous ethylene oxide." Sterilization with this gas is now widely and effectively used in hospitals. We have, therefore, designed the safe to permit gas sterilization of the needles while in the safe. This renders the radium needles available for immediate use.

Preliminary experiments[1] indicated that sterilization of radium sources was achieved in 24 hours with a concentration of 1 g./liter of ethylene oxide. Commercially, ethylene oxide is available in cylinders as a mixture containing 12 per cent by volume and 88 per cent freon. Sterilization with this mixture, after the evacuation of air from the sterilizing chamber, is routinely achieved elsewhere in 15 hours with pressures of 15 pounds per square inch (psi.) above atmosphere. Therefore, the inner safe which carries the steel plates is constructed as a gas-tight unit to withstand at least 25 psi., and is fitted with a door sealed by a rubber gasket. This arrangement is shown in Figure 7.

The inner safe is connected via a valve to a gas cylinder and via a second valve to an exhaust pipe. Ethylene oxide in the quantities used here is not toxic and the gas could be released into the room. In order to carry away possible radon contamination from leaking needles, however, the gas is vented outside the building. A safety valve set to blow-off at 25 psi. and a pressure gauge are connected directly to the safe compartment. The small volume of the safe compartment allows filling in a few seconds.

Because of the possibility that radium capsules may rupture if subjected to vacuum, the air in the safe is largely removed by a displacement method during the filling procedure. The sterilizing gas is allowed to flow slowly through the safe for a minute before the exit valve is closed. The needle holes in the plates are actually open at both ends to permit a flow of gas through them. After the safe has been filled, a few minutes are allowed for the mixing of gas and air. The gas mixture is then discharged and the safe is filled a second time, further diluting the concentration of air in the mixture. With these precautions sterility may be obtained in 24 hours with a gas pressure of 15 psi. Paper strips with B. Globigii spores have been used for bacteriologic test purposes.[1] Sterility of source plates is maintained long after the safe is opened.

IDENTIFICATION AND RECORD KEEPING

The plastic plugs which are employed for clamping the needle threads at the front end of the plates are colored according to a code which signifies the strength and active length of the needles. When the door of the safe is open, the colored pegs are visible and give an immediate indication of the safe contents (Fig. 7).

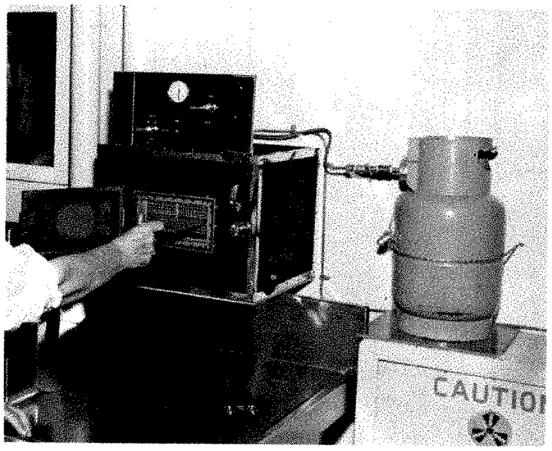

FIG. 7. Completed safe showing removal of steel plate.

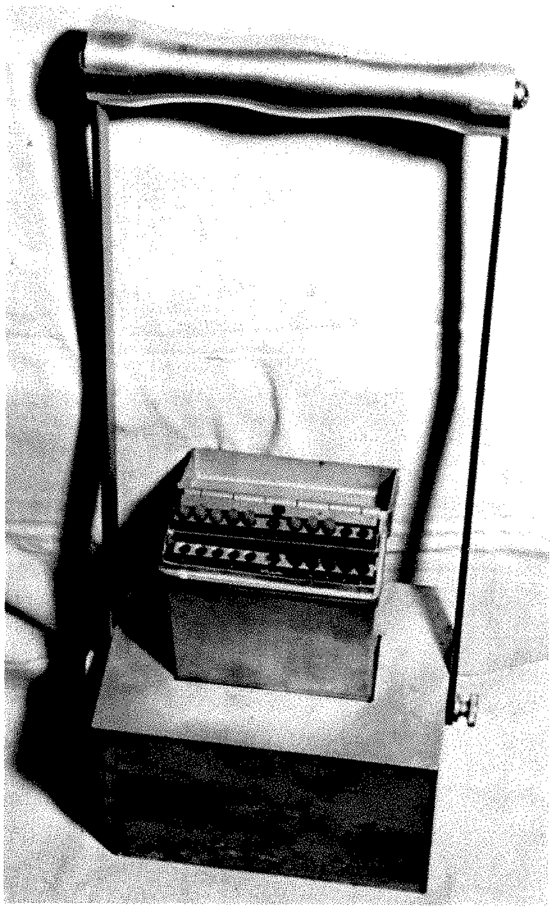

FIG. 8. Shielded carrier showing sterilizable container for transportation of loaded steel plates.

When a radium needle is in use, a colored plug becomes free. This plug is inserted, together with others released in the same treatment, into a special board alongside the patient's name and treatment schedule. Inspection of the board, therefore, indicates immediately the amount, type and location of radium in use at any time.

TRANSPORTATION OF NEEDLES

Prior to interstitial radium use, a sterile steel plate containing up to 10 threaded needles is removed from the safe, using a special handling tool (Fig. 4). The plate is rapidly transferred to a stainless steel com-

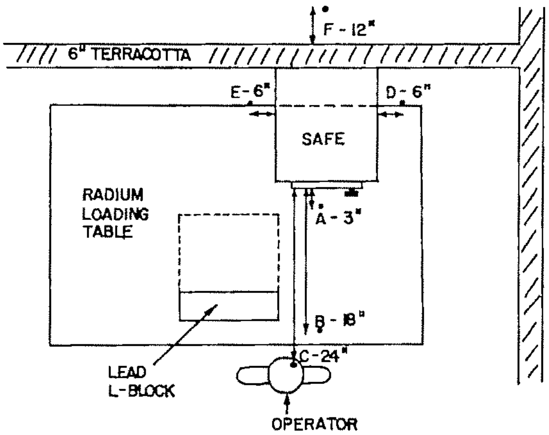

Fig. 9. Measured exposure rates in vicinity of safe containing 220 mg. of radium:

Point	A	B	C	D	E	F
mr/hr.	35	5	3	10	5	1.5

partmentalized box previously autoclaved, and is inserted with the radium end downwards. This box is similar in construction to a small section of the safe and contains four compartments. It is shown in Figure 8. The bottom of the box is immersed in a steel-encased lead block with 1 inch thick walls, which is equipped with stirrup-type handles. In order to protect the hands of the individual carrying the carrier, it is desirable to insert blank steel plates in any empty compartments. This reduces the leakage radiation exposure rate to relatively small values. Similarly blank plates should be inserted into the safe to preserve the integrity of steel shielding. The loaded carrier weighs 35 pounds.

In the operating room the carrier is deposited behind a lead shield. Needles and their associated threads may be detached from a plate behind the shield, as required.

PERSONNEL EXPOSURE

At the time of a recent radiation survey around the safe, it contained 220 mg. of radium. With the safe door closed, the exposure levels are shown in Figure 9. At the unshielded portion of an operator working at the radium loading table, the exposure rate was 3 mr/hr. At 3 inches from the closed door the rate was 35 mr/hr. With the door open, exposure rates immediately in front of the safe are doubled. The hand dose rate during plate withdrawal is about 70 mr/hr.; since this process takes less than 5 seconds, the exposure is less than 0.1 mr. With a loaded plate supported with the special tool, calculations show that the hand dose varies from 9 to 250 mr/hr. with 30 mg. of radium in the plate (Fig. 10). If the loaded plate is handled for 10 seconds, therefore, the hand exposure will be less than 1 mr.

These survey figures indicate that the shielding at the sides of the safe is very conservative. The safe could probably hold more than 1 gram of radium without exceeding any of the limits mentioned in the section on design details.

SUMMARY

A radium safe designed principally for storage of radium needles is described which has the following properties:

1. The radium is stored in a small internal space (120 cubic inches) almost entirely filled with stainless steel; this results in a small over-all size and weight.
2. The sources can be withdrawn rapidly with a minimum of handling and operator exposure.
3. There is no bulky protective door.
4. The sources are sterilized while inside the safe and, since they are already threaded, they are available for immediate use.
5. The presence of each source is separately identified; provision is made for

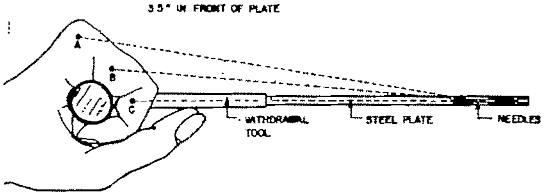

Fig. 10. Calculated hand exposure while transferring steel plate with ten 3 mg. radium sources:

Point	A	B	C
mr/hr.	250	150	9

charting the location of sources when not in the safe.

These objectives have been achieved by constructing a gas-tight storage compartment to contain stacks of closely-fitting steel plates 7 inches long in the remote end of which the radium sources are housed. The threads of needles are secured at the access end of the plates by identifying color-coded plastic pegs. The safe is sterilized by ethylene oxide maintained at a pressure of 15 psi. Lead shot is used as a shielding material.

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The authors wish to acknowledge the excellent workmanship of Mr. Oscar Fontaine in making and assembling the safe described here and the invaluable assistance of Miss Anita Mangiaracine in the bacteriologic studies.

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THE POTENTIALITIES FOR FAST NEUTRON BEAM RADIOTHERAPY*

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THE JANEWAY LECTURE of the American Radium Society for the year 1947[11] was devoted to a review of the lecturer's clinical experience with direct fast neutron beam cancer radiotherapy. The lecturer, Dr. Robert Stone, drew certain conclusions from this experience which resulted in the rather widely held view that direct fast neutron beam irradiation could not be an acceptable means of cancer radiotherapy. Dr. Stone's experience may be summarized as follows:

Two hundred twenty six patients with cancer of various anatomic sites, and generally very advanced in respect to extent and metastasis, were irradiated with a fast neutron beam and of these 17 survived 5 or more years. Observations of both immediate and late effects could, therefore, be made. Acute erythematous and, more generally, lytic effects were deliberately induced in the skin as it was felt that the fully realizable dosage had not been attained if such effects were not produced. Late, that is, occurring months and years later, changes in normal tissues were more marked than were expected in relationship to the acute reactions. These late lesions included persistent ulceration in the mouth, pharynx, and larynx, mandibular osteitis, intestinal fibrosis with rigidity and loss of control, and in 8 patients there was so much fibrotic induration in the region of the original tumor that it could not be determined whether or not residual cancer was present. None of the 17 patients surviving 5 or more years was free from distressing symptoms related to late, normal tissue-damaging effects.

At the time these clinical radiotherapy studies were performed and these clinical observations were made, certain limitations, in respect to the physics and to the radiation biology of fast neutron beams, prevailed and a radiobiological interpretation of these observations could not be made. These limitations were due to certain inadequacies of neutron dosimetry and the circumstances that the oxygen effect was not generally known; its interrelationship with linear energy transfer (LET) was unknown; and quantitative mammalian cell radiobiology had not been developed. The implications of these physical and biological factors for clinical cancer radiotherapy obviously, therefore, could not be appreciated. While the relative biological effectiveness (RBE), a term no longer useful because of lack of precision due to dose and LET dependence, was appreciated and compensated for in the neutron dosimetry, the latter was relative and dose and LET gradients in tissue or tissue-equivalent material were not developed. While the oxygen effect had already been discovered,[9] it was known only in very limited circles and not generally appreciated. While the advent of quantitative mammalian cell radiobiology has not so far resulted in the introduction of striking changes into clinical radiotherapy practice, it has resulted in the introduction of changes in the conceptual aspects of radiotherapy and a reinterpretation of Dr. Stone's experience may be attempted on such conceptual bases.

In respect to the situation obtaining today in neutron physics and radiobiology, fast neutron beam dosimetry may be absolute in the sense that calorimetric dosimetry studies can be made and depth dose distributions may be determined in water or in tissue-equivalent material.[8] The oxygen effect and its interrelationship with LET have been studied in quantitative mammalian cell systems both by ourselves[1] and by others. It can now be stated formally that there is a continuously variable inverse relationship between the oxygen effect ratio and LET with limiting values of the former of near 3 at low values of LET and of near 1 at high values of LET (Fig. 1). Our quantitative mammalian cell radiobiology studies of fast neutron irradiation have shown that there is no recovery phenomenon associated with fractionated doses at the highest level of LET studied, that of fission spectrum fast neutrons.[2] This means that, at the highest LET level of fast neutron irradiation studied, the mammalian cell survival curve is fully exponential, that fractionated doses are fully cumulative in their cell killing effects, and that there is no sublethal injury associated with the highest LET fast neutron irradiations in the sense of the recoverable injury of low LET x-ray and gamma-ray irradiations. A reinterpretation of the experience of Dr. Stone may now be attempted on the bases of the physical and radiobiological considerations developed above.

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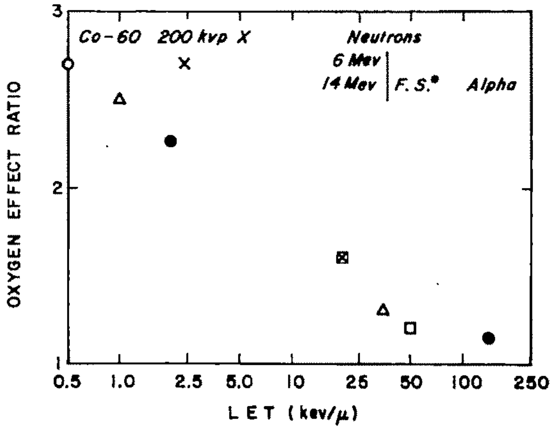

* Fission Spectrum

Fig. 1. The interrelationship of the oxygen effect and LET for mammalian cells.

Oxygen Effect Ratio: The ratio of the reciprocal of the D_0 dose for the oxygenated condition of irradiation to that for the anoxic condition.

□Andrews, J. R., Correa, J. N., and Belli, J. A. (Fast neutron irradiation, cell reproductive capacity, and the oxygen effect. Proc. Symp. Internat. Atomic Energy Agency on the Biological Effects of Neutron Irradiations. Internat. Atomic Energy Agency, Vienna, Austria, 1964.)

●Barendsen, G. W., and Walter, H. M. D. (Differences between densely and sparsely ionizing radiations with regard to modification of radiation damage in human tissue culture cells. In Review by L. F. Lamerton, Linear Energy Transfer. Radiation Effects in Physics, Chemistry and Biology, M. Ebert and A. Howard, Ed., Amsterdam; North-Holland Publishing Company, pp. 1–13, 1963.)

○Belli, J. A., and Andrews, J. R. (The relationship between tumor growth and radiosensitivity. *J. Nat. Cancer Inst.*, 1963, *31*, 689–703.)

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△Schneider, D. O., and Whitmore, G. F. (Comparative effects of neutrons and x-rays on mammalian cells. *Radiation Res.*, 1963, *18*, 286–306.)

The radiation injury of overlying normal tissues was especially severe. This may be attributed, in part at least, to LET gradients, from a higher LET superficially to a lower LET deeply and to a nonrecoverable type of cellular injury. The cyclotron-produced fast neutrons used by Dr. Stone had energies ranging from 0 to 19 mev. The lower energy fast neutrons are less penetrating than the higher and the former have a higher mean LET.[10] Thus, not only would the greatest dose have been given in the superficial layers, but this dose would have been given at the highest levels of LET in the beam. Dr. Stone, himself, had observed that biological effects related to neutron energy, and, therefore, to LET, existed for he determined that for the production of the same degree of skin erythema a higher dose was required for neutrons generated by a 16 mev. deuteron than for those generated by an 8 mev. deuteron beam. The possible clinical significance of the differences in the recovery factors associated with high LET fast neutron radiations and with low LET x-rays and gamma-rays is very difficult to evaluate. When a scatter diagram, developed from Dr. Stone's published data,[12] is constructed showing the interrelationships of the degrees of the skin reactions of the face and neck, the total skin field doses, and the total elapsed time in days, there seems to emerge a pattern from which one may infer a direct relationship between the severity of the cutaneous reactions and the total skin dose but which suggests that the severity of the reactions is independent of the time, 8 to 64 days as the study was performed, in which this total dose was administered. The latter suggests, of course, the possible absence of recovery phenomena between dose fractions. The evaluation of a possible oxygen effect is very difficult. This is due, in part, to the reason that the oxygen effect actually has not so far been evaluated in relationship to x-ray or gamma-ray human cancer radiotherapy. Dr. Stone did conclude, however, that there was not a significant difference between the doses required to destroy cancers and those causing severe damage to normal tissues. It has recently been shown[14] that under irradiation conditions resulting in the induction of equal cancericidal effects on a mouse transplantable tumor when the irradiations were performed under conditions of either air at ambient pressure, high pressure oxygen, or tourniquet anoxia with appropriate adjustments of x-ray dose for the induction of these equal cancericidal effects, the skin reactions were less by a factor of from 3 to 4 for the conditions of hyperoxia or anoxia than for the condition of air breathing at ambient pressure. If, then, the most important radiosensitivity differences observed in human normal and cancer tissues are due to the oxygen effect alone (for discussion of this see reference 1) and if the neutron irradiations employed by Dr. Stone were relatively independent of the oxygen effect, then the ratio of the doses required to destroy the cancer to those causing severe damage to normal tissues should have been small in respect to that which was actually observed.

In summary, thus far, it may be stated that there are certain quantitative and qualitative human normal and cancer tissue irradiation responses associated characteristically with LET and the oxygen effect. The LET effects result in changes in apparent radiosensitivity and in cellular recovery phenomena and, therefore, in the restitution of tissue cell population numbers, and the oxygen effect is inversely related to LET. High LET radiations are relatively independent of this oxygen effect, and, if the effect is important in human cancer radiotherapy, then high LET radiations may be used to circumvent it. Changes in the cellular recovery phenomena associated with high LET radiations will have to be very carefully considered in any subsequent clinical study of human cancer fast neutron beam radiotherapy in respect to both the size and spacing of dose increments.

It is anticipated that the application of a cyclotron-produced fast neutron beam to human cancer radiotherapy will again be studied.[5] It has already been indicated that the LET gradients characteristic of such a beam may be undesirable. Higher energy monoenergetic neutron beams would provide both better depth dose distributions and LET gradients. Such a beam of possible clinical usefulness would be the 14 mev. monoenergetic fast neutron beam produced at deuteron accelerating voltages of a few hundred kev. by the $H^3(d,n)He^4$, or D-T, reaction. The oxygen effect ratio for such a beam has been shown to be essentially the same as that for the cyclotron-produced beam (Fig. 1). Depth dose distributions for both the 14 mev. monoenergetic and the cyclotron-produced 0–19 mev. neutron energy spectrum fast neutron beams are shown and compared with medium voltage x-ray and cobalt 60 beams in Figure 2. The neutron data cannot be considered to be absolute but they do represent the best presently available. Recent technological developments suggest that a 14 mev. neutron generator may be produced with a high enough flux to be useful for clinical cancer radiotherapy with physical dimensions of a very small size, with deuteron accelerating voltages of only a few hundred kev., and at a price competitive with cobalt machines.[7]

The question of the use of fast neutron beams as sources of ionizing radiations (for a discussion of the energy transfer processes involved see reference 1) for human cancer radiotherapy ultimately concerns itself with problems of dose distribution, cellular recovery factors, and the oxygen effect. It would appear from Figure 2 that a satisfactory dose distribution for human cancer radiotherapy could be obtained with a 14 mev. monoenergetic fast neutron beam. The importance of cellular recovery factors in human cancer radiotherapy is related to the kinetics of the postirradiation restitution of the cell populations of both normal and cancer tissues. It is apparent that a given fractionated dose of high LET radiations, these being fully cumulative in their cell killing effects, will have a greater depleting effect on normal cell populations than will the equivalent fractionated dose of low LET radiations, x-rays or gamma-rays, which are not fully cumulative in their cell killing effects, and that this difference will be magnified in repeated, small dose fractionation. This may be a very important consideration where relative radiation effects on those normal tissues, principally the mucous membranes and hemopoietic tissues, having short cell population turnover times and relatively small stem cell populations, and on those cancers, principally epithelial cancers, having relatively large stem cell populations and long cell population doubling times, are concerned.

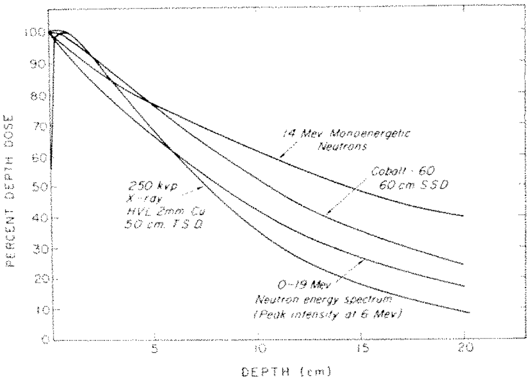

Fig. 2. Relative depth dose curves.

Cobalt 60 gamma rays. (British Institute of Radiology, Depth Dose Tables for Use in Radiotherapy. *Brit. J. Radiol.*, Suppl. 10, 1961.)

250 kvp. x-rays. (*Brit. J. Radiol.*, Suppl. 10, 1961.)

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0–19 mev. neutron energy spectrum, peak intensity at 6 mev. (Bewley, D. K. Physical aspects of the fast neutron beam. *Brit. J. Radiol.*, 1963, *36*, 81–88.)

The importance of the oxygen effect in human cancer radiotherapy rests upon the assumption that there are cells in human cancers which, at the time of irradiation, are severely hypoxic or anoxic and which are, therefore, at the lowest level of radiosensitivity but which are, nevertheless, capable of survival with unlimited reproductive capacity. We[3] have developed evidence supporting the validity of this assumption. The P388 lymphocytic leukemia of the DBA mouse when grown as an ascitic tumor becomes severely hypoxic or anoxic after 3 days of growth following the interperitoneal inoculation of one million cells. The anoxic state persists for the next 4 days and the tumor cells continue to proliferate, although at a slower rate after the fourth day. The number of unirradiated cells required to transplant the tumor into other recipient animals does not change from the first to the 7th day of growth despite the fact that the population has changed from an oxygenated to an anoxic one after the third day. These findings mean that cell reproductive capacity has not been impaired by sustained anoxia. Other evidence of the importance of the oxygen effect includes the work of van den Brenk *et al.*[14] already cited, of du Sault,[4] and of Goldacre and Sylvén.[6] Du Sault irradiated spontaneous tumors of mice with x-rays while they were breathing either oxygen at 3 atmospheres of pressure, 95 per cent oxygen and 5 per cent carbon dioxide at 3 atmospheres, or 95 per cent oxygen and 5 per cent carbon dioxide at 1 atmosphere, and all conditions gave the same cure rate without increasing the normal tissue reactions over those occurring when performing the irradiations while they were breathing air at ambient pressure. Goldacre and Sylvén studied the distribution of a diffusable dye, lissamine green, into transplantable cancers of rodents and determined that there were uncolored zones of tumor cells into which the dye did not diffuse but from which tumor cells could be dissected which produced tumor implants in other animals. The presence of uncolored zones suggests that there is impairment of the blood supply, of diffusion phenomena, or of both with, possibly, anoxia but not cell death as cells from these zones could produce tumors. Direct clinical evidence of the importance of the oxygen effect in human cancer radiotherapy by the use of high pressure oxygen irradiation chambers has been very difficult to obtain because of the rigid requirements of a statistically significant study. Van den Brenk[13] has irradiated some 250 patients with advanced cancer with 4 mev. x-rays under high pressure oxygen. Eighty-four of these patients had comparable, advanced cancer of the head and neck with lymph node metastases in the neck. Three months after irradiation 56 of 59 high pressure oxygen and 11 of 25 conventionally irradiated cases had complete retrogression of the presenting cancer to the same pattern of dose fractionation and total dose. Stone and Larkin[12] published initial observations on 120 patients presenting with a variety of far-advanced cancers and without any process of selection or case matching. Twenty-six of the 120 had complete regression of the presenting primary tumor 3 months after irradiation and 53 had partial regression. It is apparent that no definite conclusions regarding the circumvention of the oxygen effect by irradiation with fast neutrons can be drawn from these data but these are the best which are presently available.

CONCLUSION

The experience of Dr. Stone with fast neutron beam cancer radiotherapy has been re-examined and reinterpreted in the light of contemporary neutron physics and cellular radiation biology. Such a reinterpretation suggests physical and radiobiological reasons for both the undesirable radiation effects which were observed by Dr. Stone and, also, the desirability of mounting additional fast neutron beam human cancer radiotherapy studies, especially with 14 mev. monoenergetic neutrons. Finally, the present status of both neutron physics and radiobiological concepts permits a re-exploration of the usefulness of fast neutron beam human cancer radiotherapy with the probable elimination of some of the risks and undesirable sequelae which were encountered by Dr. Stone in his study.

ADDENDUM

In the design of human cancer radiotherapy facilities certain problems which are inherent in such facilities must be solved regardless of the type, photon or particle, or energy, low or high, of the radiation employed. These common problems are concerned with the precise orientation of the patient and the radiation beam, the collimation of the beam, the shielding of personnel and of those parts of patients where radiation is undesirable, and the attainment of a clinically convenient dose rate. These same problems have to be solved before the introduction of 14 mev. fast neutron beam radiotherapy into clinical practice is feasible and a possible solution of them is suggested in Figure 3.

Means for the precise orientation of the patient, when the patient is enclosed in a chamber, and the radiation beam by the prior use of a simulator have already been developed in detail in respect to high pressure oxygen radiotherapy.[18] Problems of beam collimation and shielding have been considered in detail[15] and may be solved by the development of such a facility as suggested by Figure 3. It appears that advances in target technology[16,17] will permit the attainment, in the very near future, of a clinically convenient dose rate of 14 mev. fast neutrons.

The separate solutions of these several general problems may, then, be combined in the single facility suggested in Figure 3. The patient is irradiated in a cylinder lying in a block of paraffin. Beam-defining collimator inserts composed of steel and paraffin and of appropriate size and shape may be selected from the dolly to be placed in the collimator insert port of the internal ring. The neutron generator is fixed to the external ring and both rings move concentrically and independently of one another around the patient-containing cylinder. The cylinder itself could be, of course, a tank into which gases could be introduced under pressure.

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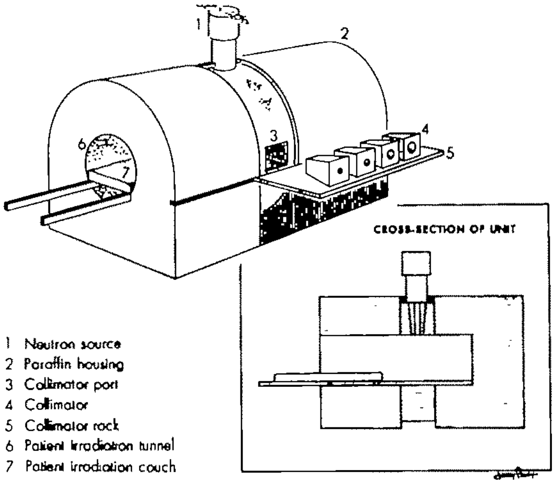

Fig. 3. Suggested solution of problems associated with the development of a 14 mev. fast neutron beam human cancer radiotherapy facility.

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BIOPHYSICAL CONSIDERATIONS CONCERNING THE EXISTENCE OF A THRESHOLD DOSE FOR RADIATION EFFECTS*

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THE risk attendant to exposure to low doses of ionizing radiation ultimately depends on whether there is a threshold dose for the induction of radiation injury. It would appear that the results of recent research in radiation biology and in radiological physics may be combined to provide rather definite conclusions concerning the existence of a threshold dose for the killing of the mammalian cell by low LET (linear energy transfer) radiation such as conventional x- and gamma rays.

In the case of high LET radiation there is no reason to believe that a threshold exists. In all cells investigated thus far, inactivation at low doses must be proportional to dose because inactivation occurs in single events. This conclusion is based not only on the 2 classic criteria of an exponential dose effect curve and independence of the effect on dose rate, but also on the recognition that in fact only one particle is required to inactivate the cell. Figure 1 shows dose effect curves for both high and low LET radiations and for two different types of mammalian cells. One pair was obtained for human cells in tissue culture,[1] the other for late A and B type spermatogonia of the mouse.[3]

In the case of α particle irradiation of the tissue culture cells, the authors have calculated that the inactivation cross section per particle is equal to the geometric cross section of the nucleus, leading to the rather natural inference that a single particle crossing the nucleus will inactivate the cell. In the case of the even more sensitive spermatogonia, it can be shown that one high LET particle (usually a proton) traversing the cell will kill it even if the trajectory does not take it through the nucleus (see appendix). The implied existence of vital radiation-sensitive cell components in the cytoplasm may be related to the complex division kinetics of these cells, some of which differentiate into other precursors of mature sperm while the remainder return to the status of stem cells. However, whatever the reason, such sensitivity would appear to be unique and it would be reasonable to assume that most other cell lines fall into the well established pattern of high sensitivity of the nucleus only. It may thus be assumed that in either instance inactivation occurs through the agency of a single high LET particle.

It is evident that inactivation by low LET radiation proceeds in a more complex manner in both cell types. The detailed shape of such curves has been attributed to either a multi-target inactivation[6] which should result in a curve leaving the 100 per cent survival point on the ordinate at right angles and turning into a straight exponential section which may be extrapolated to obtain the "hitness" number; or a multi-hit relation[1] which should exhibit neither of these characteristics but, nevertheless, could have a very similar shape. In the former case the survival curve is given by

$$S = 1 - (1 - e^{-\alpha D})^N,$$

in the latter case by

$$S = e^{-\alpha D} \sum_{x=0}^{N-1} \frac{(\alpha D)^x}{x!}.$$

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Here α is the inactivation constant, D the absorbed dose and N the multiplicity of targets or hits.

The multi-target and the multi-hit theories are both based on the assumption that the cell contains certain *sensitive sites* and that inactivation of the cell requires a minimum of energy absorption in such sites. According to the multi-target concept, several closely neighboring sites must all receive a minimum of energy and this usually occurs at least once when a high LET particle traverses the cell, whereas a high speed electron deposits sufficient energy in only one of these related sites. According to the multi-hit model, sites are not related but the energy required for their inactivation is sufficiently high so that an electron can not lose enough in a single traversal, although a high LET particle can.

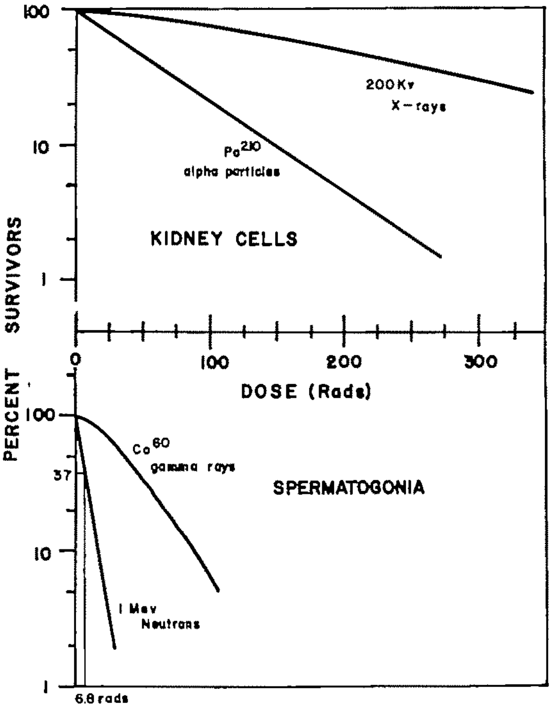

Fig. 1. *Top.* Survival curves for human kidney cells in tissue culture irradiated by Po^{210} alpha particles and by 200 kv. x-rays. (After Barendsen *et al.*,[1] 1960.) *Bottom.* Survival curves for late type A and type B spermatogonia irradiated by 1 mev. neutrons and by Co^{60} gamma rays. (After Bateman *et al.*,[3] 1960.)

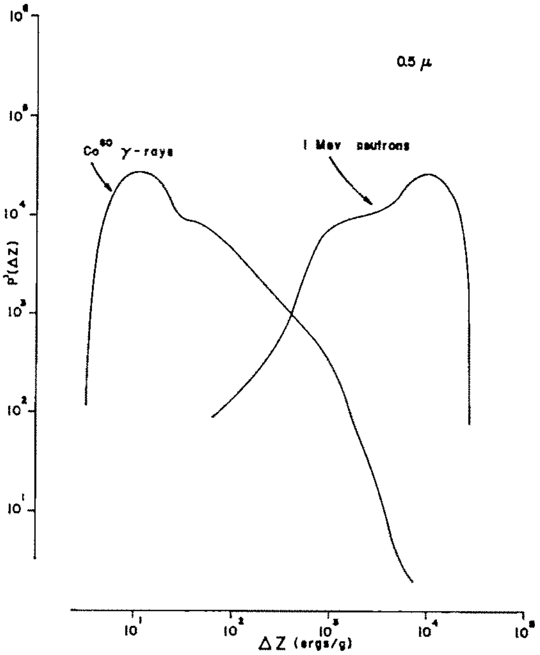

Fig. 2. $P'(\Delta Z)$ the probability of ΔZ per unit logarithmic interval of ΔZ. ΔZ is the increment of energy density produced by an individual charged particle and its secondaries in a small tissue sphere. The sphere diameter is 0.5 microns and the radiations 1 mev. neutrons and Co^{60} gamma rays. (After Biavati,[4] 1963.)

In the simplified form given above, neither of these approaches takes adequate account of the great variability of the amount of energy that may be locally deposited by charged particles and, in particular, by electrons. Differences in LET, delta ray production, and track curvature may in combination produce very wide variations of ΔZ, the increment of local energy density. This has been defined[8] as the energy deposited by a charged particle and its secondaries divided by the mass of tissue of a spherical volume in which this energy has been deposited.

Figure 2 shows the probability of ΔZ as a function of ΔZ for the radiations employed in the spermatogonia experiment. The distributions are for a 0.5 micron diameter sphere of tissue and because of the wide range of ΔZ values and their probabilities logarithmic scales have been chosen for both coordinates. It will be seen that the distributions span several decades of ΔZ and that there is a very definite overlap even within the range of frequencies covered by these experimental data. It follows that electrons produced by cobalt 60 gamma rays can in a 0.5 micron diameter sphere of tissue occasionally deposit an energy increment that is comparable to the energy typically lost by the protons liberated by 1 mev. neutrons. The probability of this occurring is obviously small but certainly not negligible.

The 0.5 micron diameter chosen in this example represents the smallest diameter for which reliable data are available at present. However, an extrapolation of existing data as well as theoretic considerations indicate that for smaller sizes the overlap would become even more pronounced because of an increased spread of energy loss due to statistical fluctuation. Conversely, the overlap at larger sizes is less but even at diameters of a few microns it is still quite detectable.

According to present theories, the volume from which the energy instrumental in the inactivation of sensitive sites is abstracted is smaller than that of a 0.5 micron diameter sphere because there are no recognized mechanisms of energy migration over such large distances. However, the volume to be associated with sensitive sites is certainly subject to speculation and the same applies to any energy requirements for inactivation and the number of sites per cell. For these reasons, it is so far impossible to derive with any degree of assurance the shape of the dose effect curves at low doses of gamma radiation from physical data of the type shown in Figure 2. However, because of overlap of ΔZ spectra, it would appear that for low LET radiation there must also be a finite slope of the dose effect curve near the origin no matter what the pertinent parameters may turn out to be. Since the energy required for injury is probably less, and certainly not much more than that required for killing, these considerations should also apply to nonlethal damage, which is far more important than cell death in low level chronic exposure.

These considerations are therefore of significance in radiation protection. However, it must be stressed that they apply to the cell and not necessarily to tissues or organisms. While it may be assumed with a certain degree of confidence that certain effects of low level irradiation originate in individual cells (such as mutations) and others in many cells (such as cataracts), the question as to whether the condition originates in a single cell has yet to be unequivocally answered for such important effects as carcinogenesis. Once several cells must be affected, the already low probability for injury must be raised by an exponent which is equal to the number of cells involved and consequently the probability of such injury would be very much smaller.

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APPENDIX

PARTICLE DENSITY IN SPERMATOGONIA AT LD_{37} FOR 1 MEV. NEUTRONS

As seen in Figure 1, the LD_{37} for mouse spermatogonia irradiated by 1 mev. neutrons is 6.8 rads. In a first order inactivation, the average number of events (*i.e.*, particles per cell) is one at the 37 per cent inactivating dose. The question may thus be asked: "How large a volume will on the average be traversed by one particle if tissue is irradiated by 6.8 rads of 1 mev. neutrons?" The ratio of this volume and the volume of the cell represents the fraction of the cell in which inactivation can occur by a single particle.

It can be shown[7] that F, the average number of events per rad of absorbed dose, is given by

$$F = \int_0^{Y_{\max}} \frac{D(Y)d^2}{30.6Y}\, dY,$$

where d is the sphere diameter and

$$Y = \frac{\Delta Z d^2}{30.6}$$

is the energy laid down in individual events divided by the sphere diameter. $D(Y)$ is the fraction of the dose expended at Y.

Since F represents the frequency per rad and the LD_{37} is 6.8 rads, the frequency of particles at LD_{37} is 6.8 F.

The distribution, $D(Y)$, for 1 mev. neutrons and for a number of values of d has been published.[5] Table 1 shows values of 6.8 F as a function of d. It will be noted that, even for the largest diameter investigated, the frequency of events at the LD_{37} is still less than 1. Measurements at other energies have been carried out up to values of d which are 12 microns. Using these values as a guide, it would appear that 6.8 F becomes 1 for a diameter of approximately 8.5 microns. A number of measurements[2] of sections indicate that these spermatogonia are ellipsoids, having major and minor diameters of 5.5 and 3.0 microns, respectively. Although it is likely that fixation introduces shrinkage, it seems quite unlikely that the nuclei could be equivalent to 8.5 micron spheres in the animal.

Table I

FREQUENCY OF EVENTS AT LD_{37} FOR SPERMATOGONIA IRRADIATED BY 1 MEV. NEUTRONS AS A FUNCTION OF SPHERE DIAMETER

Tissue Sphere Diameter (μ)	Frequency of Events per 6.8 Rads (6.8 F)
0.55	1.97×10^{-3}
1.30	1.19×10^{-2}
2.76	6.23×10^{-2}
6.00	3.41×10^{-1}

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RADIATION HEPATITIS*

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THE liver is generally considered a relatively radioresistant organ. In 1942, Warren[16] reviewed the remarkable variety of results from animal work reported in the earlier literature and stated that "one could draw no definite conclusion as to the sensitivity of human liver to irradiation." Warren also discerned no correlation between the dose of radiation and the degree of hepatic injury.

The first report of an effect of irradiation on the human liver was by Case and Warthin[6] in 1924. These authors reported inflammation of the bile duct epithelium, with little change in the blood vessels or hepatic cells. Since that time, there have been only a few reports of histologic changes in the liver following irradiation. Brick,[5] in 1955, studied 9 autopsy specimens of liver following radiation therapy. In most of these cases, more than 5,000 r was delivered to the left lobe of the liver. The commonest finding was necrosis of the liver and in 3 cases fibrosis was marked. Phillips *et al.*[13] reported 36 cases of whole liver radiation therapy for known metastatic disease. The tumor dose ranged from 2,000 to 3,750 r. In only 1 patient was radiation damage of the liver suspected; this followed 3,500 r. Nowhere is there a correlation between the clinical picture and histologic findings following radiation therapy to the entire liver.

During the past 4 years at Stanford University Medical Center, Division of Radiotherapy, we have undertaken to irradiate the entire liver in 40 patients. These patients had 2 types of malignant disease: (1) disseminated ovarian carcinoma, and (2) lymphomas with known abdominal disease.

In carcinoma of the ovary, peritoneal implantation makes it important to treat the entire peritoneal surface of the abdomen when there is any evidence of spread of disease outside of the pelvis. In doing this, one must treat all of the liver, as it has visceral peritoneum over almost its entire surface. In the lymphomas, the frequency of hepatic spread of the disease is well known, both with and without evidence of para-aortic lymph node metastasis.

Levitan *et al.*[8] observed that 87 per cent of patients with Hodgkin's disease of the liver coming to autopsy had diffuse involvement of the liver with the disease. These authors further state that of 57 patients coming to autopsy with the diagnosis of Hodgkin's disease and jaundice, the jaundice was due to Hodgkin's disease involving the liver parenchyma alone in 70.2 per cent and to extrahepatic biliary obstruction by tumor in only 3.5 per cent. Bouroncle *et al.*[4] reported a similar series showing 9.7 per cent incidence of extrahepatic biliary obstruction by tumor, and 45 per cent with diffuse hepatic involvement producing the jaundice. We believe that lymphomatous involvement of the liver can be controlled with radiation therapy and it would seem from the above studies that when there is evidence of liver involvement with lymphomas, it is preferable to treat the entire liver if this can be done effectively and safely. Phillips *et al.*[13] recommend treating the entire liver for palliation of hepatic metastases from the breast, bronchus, and gastrointestinal tract.

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TREATMENT DATA

The treatments have been carried out with the Stanford medical linear accelerator,[7] and, more recently, with a Varian Clinac, the former having an energy of 5.3 mev. and the latter 6 mev. When treating the entire abdomen, two adjoining fields of about 20×25 cm. have been used. As can be seen in Figure 1, all of the liver is included in such fields. In about one-third of the patients, lateral fields were used in addition to the anteroposterior ports. In ovarian carcinoma patients, who received radiation to the entire abdomen, the kidneys were shielded at approximately 1,500 rads and the pelvis was carried to 5,500 rads. The daily increments used were 100–200 rads.

The dose to the entire liver has ranged from 1,300 rads in 18 days to 5,100 rads in 40 days. The median dose was 3,900 rads. The isodose distribution is seen in Figure 2. In addition to these 40 patients who received radiation to their entire liver, we have pre- and postirradiation histologic material on a smaller group of patients who received 5,500 rads to the left lobe of the liver only. These were patients with carcinoma of the esophagus who had biopsy-proven epigastric metastases. In order to treat this area, we included a portion of the left lobe of the liver in our field.

Patients have tolerated such massive treatment as described for ovarian carcinoma surprisingly well. Transient nausea, vomiting and diarrhea have occurred, but in no case have these required termination of the proposed treatment plan. Leukopenia and thrombocytopenia also occur and usually are self-correcting with a 3 or 4 day interruption of treatment. In no instance has there been any evidence of liver dysfunction or injury manifesting itself while the patient was actually under treatment. None of these patients received prior or concomitant chemotherapy.

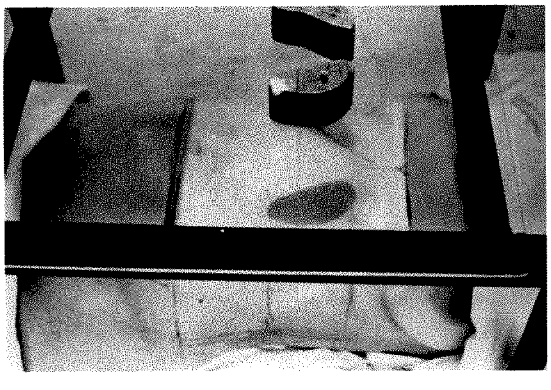

Fig. 1. A typical upper abdominal field used in treating patients with ovarian tumors. As can be seen, the entire liver is included in such treatment. "Shadows," cast by lead blocks, are used to protect the kidneys after 1,500 rads.

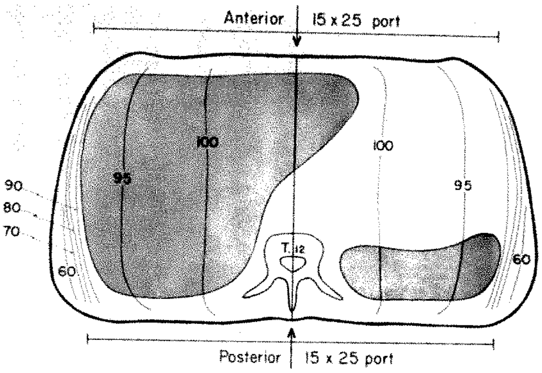

Fig. 2. Isodose distribution to the upper abdomen at the level of T12 when large anterior and posterior ports (15×25 cm.) are used. The dose to the liver is homogeneous.

CLINICAL FINDINGS AND INCIDENCE

We have noted, however, and wish to describe here, a group of clinical observations and histologic findings which we believe are caused by irradiation of the liver. The term "hepatitis" is used only for convenience, as in radiation pneumonitis and radiation nephritis, and is not meant to imply an inflammatory response of the liver. The clinical picture characteristically has its onset 2 to 6 weeks following completion of radiation therapy to the liver. The severity of symptoms and findings varies markedly, but usually the patient complains of rapid weight gain and increase in abdominal girth. Physical examination consistently reveals an enlarged liver and varying amounts of ascites. Laboratory studies show abnormalities of most of the liver function tests including the serum enzyme levels. The serum alkaline phosphatase has

TABLE I

INCIDENCE OF HEPATIC INJURY IN 40 PATIENTS TREATED WITH IRRADIATION OF THE ENTIRE LIVER, USING FROM 1,300 TO 5,100 RADS

Clinical diagnosis alone	6/13
Clinical diagnosis with needle biopsy substantiation	7/13
Total incidence	13/40

been the single most reliable laboratory index.

We have employed the following criteria for the diagnosis of radiation hepatitis in any patient whose subsequent course showed them to be free of clinically significant hepatic metastases and who after irradiation of the entire liver develops: (1) significant alteration of liver function tests; (2) previously undetected hepatomegaly; (3) onset of ascites; or (4) a needle biopsy of the liver showing what we have come to recognize as radiation-induced liver changes, to be described later.

In our series of 40 patients receiving irradiation to the liver, 13 patients met the above criteria. In 6 cases the diagnosis was based on physical findings and laboratory studies alone, and in 7 additional cases the diagnosis was substantiated with a liver biopsy (Table I).

There appears to be a relationship between radiation dose and the induction of this syndrome; the greater the dose of radiation, the higher the incidence of functional and histologic hepatic changes. Figure 3 shows the dose distribution in our 40 patients, with the case of radiation hepatitis being indicated. It can be seen that below 3,000 rads there are no cases, while above 4,000 rads, 3 out of 4 patients treated had evidence of liver dysfunction. In the 3,800–4,000 rad range, 7 of 17 patients treated, or 42 per cent, showed the effects of hepatic irradiation.

TREATMENT

There were all grades of severity of hepatic insufficiency secondary to irradiation. Some patients were asymptomatic and required no treatment. Other patients received conservative care as out-patients, while still others, in spite of vigorous hospital care, expired due to hepatic failure.

Three case histories are reported to illustrate the variations in disease severity and outcome, as well as modes of treatment.

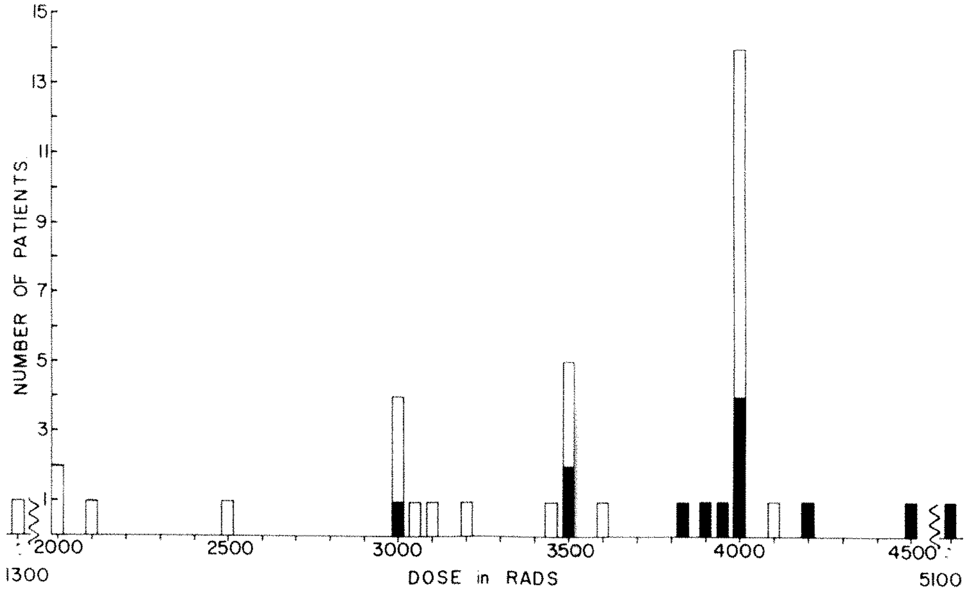

FIG. 3. Dose distribution in 40 patients treated with irradiation of the entire liver, using 1,300 to 5,100 rads. The incidence of radiation hepatitis appears related to the dose of hepatic radiation given. □ = Total number of patients; ■ = radiation hepatitis.

REPORT OF CASES

Case i. A 52 year old female had had a bilateral salpingo-oophorectomy for carcinoma of the ovary with operative spillage of a cystic tumor. Before radiation therapy the liver was not enlarged. The patient started treatment on March 22, 1962, and received 5,500 rads to the pelvis in 50 days and 4,000 rads to the entire upper abdomen (including the whole liver) in 58 days using a four-field technique. Following completion of therapy the patient got along well for 10 weeks. At that time she reported a 10 pound weight gain, and increase in her abdominal girth. Soon thereafter the liver was found to be 4 cm. below the right costal margin. The alkaline phosphatase was 5.4 Bessey-Lowry units (normal: 0.8–2.8), and the serum glutamic pyruvate transaminase 54 units (normal: 0–35). The patient was treated as an out-patient and received diuretics for about 6 months. At the present time, approximately 1½ years after first detecting evidence of liver damage, the patient is taking no diuretics, has no ascites, the liver is not enlarged, the serum glutamic pyruvate transaminase is 15 units, but the alkaline phosphatase is still elevated to 4.9 Bessey-Lowry units.

Comment. We believe that this patient represents a case of minimal acute radiation hepatitis responding well to diuretics and conservative care.

Case ii. A 47 year old female at celiotomy was found to have a large, nonresectable retroperitoneal epigastric mass. The histology was reported as reticulum cell sarcoma. Mediastinal lymphadenopathy was also present. The liver was not enlarged and all liver function tests were within normal limits. Radiation therapy was started on February 18, 1963, and the patient received 3,900 rads to the upper abdomen (including the entire liver) in 71 days. There was a 37 day interruption of the treatment to her liver at 2,000 rads so that we might treat her increasingly symptomatic mediastinum. At the completion of this prolonged course of therapy, the liver was thought to be enlarged. Two weeks later the patient had very pronounced ascites, the liver was palpable 12 cm. below the costal margin, but she did not appear jaundiced. The alkaline phosphatase was 10.6 Bessey-Lowry units, the serum glutamic pyruvate transaminase 16 units, and the total bilirubin 0.8 mg. per cent.

The patient was hospitalized, a paracentesis and liver biopsy were performed, and she was treated with bed rest, high protein and high caloric diet, and diuretics including spironolactone (Aldactone A). After 1 month of the above therapy, the patient was discharged on diuretics and reduced activity at home. Now, 9 months following discharge from the hospital, she is off diuretics and is without ascites. Her liver is still 8–10 cm. below the costal margin, the alkaline phosphatase is 14.0 Bessey-Lowry units, and the serum glutamic pyruvate transaminase 15 units. A repeat liver biopsy has been obtained within the past month. The patient also has evidence of metastases to the lymph nodes in the right axilla and groin at this time which are responding to chemotherapy.

Comment. This patient represents a case of considerably more severe radiation hepatitis requiring hospitalization for more vigorous therapy, and evidence of chronic hepatic impairment 10 months later. The first liver biopsy was obtained upon admission to the hospital, 17 days following completion of radiation therapy to the liver. It showed hemorrhage and sinusoidal congestion with erythrocytes, which we have come to associate with the typical pattern of acute radiation hepatitis. The most recent biopsy was obtained 10 months following completion of treatment and shows only mild fatty infiltration. These histologic findings will be discussed in detail in another section.

Case iii. A 52 year old male had had a celiotomy because of the sudden onset of jaundice. The patient was found to have reticulum cell sarcoma involving the lymph nodes at the hilus of his liver (producing the obstructive jaundice) and the entire mesentery, as well as lymphomatous invasion of the jejunum. A cholecystojejunostomy was performed with resection of a portion of the jejunum. The alkaline phosphatase was 5.6 Bessey-Lowry units, and the liver was not enlarged. We then treated the patient's upper abdomen (including the entire liver) with a four-field technique to 3,850 rads in 37 days. The kidneys were shielded at 1,500 rads. Five weeks after the completion of therapy, the patient was readmitted to this hospital with jaundice, ascites, liver palpable 6 cm. below the costal margin, alkaline phosphatase of 5.5 Bessey-Lowry units, serum glutamic oxalacetic transaminase of 93 units (normal: 0–40) and total bilirubin of 1.8 mg. per cent. A thoracentesis, paracentesis, and liver biopsy were performed. The patient was treated vigorously with salt restriction, high caloric and protein diet, bed rest, diuretics, including spironolactone (Aldactone A) and steroids. After approximately 2 months of the above program, the patient seemed to be doing fairly well. He was not reaccumulating ascitic fluid, his liver function tests remained unchanged relative to their levels on admission, his liver was still palpable 2–4 cm. below the costal margin, and he seemed to be gaining weight in muscle mass. He was then discharged to his home in another part of the state. He did well for 1 month and then began to reaccumulate progressively increasing amounts of ascitic fluid, ultimately requiring repeated paracenteses. One month later, the patient died of fluid and electrolyte imbalance and renal failure. At autopsy, no tumor was found. The liver weighed only 900 gm. and the capsule was wrinkled. The cut surface showed extensive hemorrhage and was cobblestoned in appearance.

Comment. This represents a case where in spite of vigorous therapy, massive ascites, caused by radiation-induced hepatic insufficiency, persisted and resulted in death.

The liver biopsy obtained early in the course of the disease showed the typical changes of acute radiation hepatitis and was indistinguishable from that of Case II. The histologic findings at autopsy are quite different from the late changes seen in Case II and will be discussed in the next section.

PATHOLOGY

Histologic material is available in 17 cases which have had radiation to the entire liver, as well as 3 cases which have had 5,500 rads to the left lobe of the liver only. The majority of liver specimens obtained

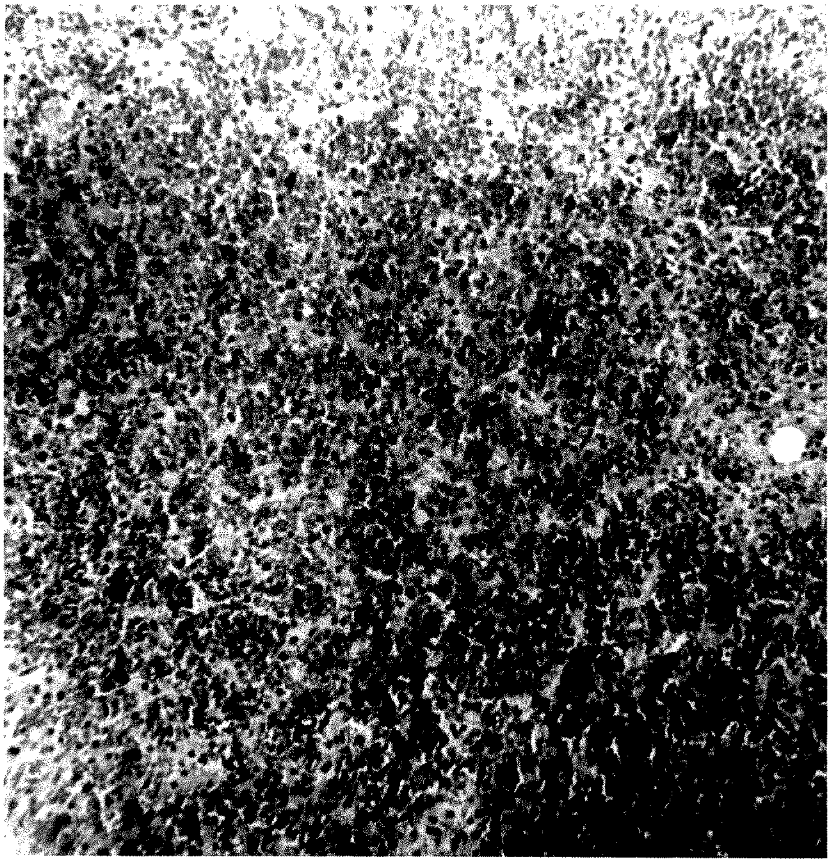

FIG. 4. Case II. Needle biopsy of patient with clinical signs and symptoms of acute radiation hepatitis obtained 17 days following 3,900 rads shows extensive central sinusoidal congestion (H&E×200).

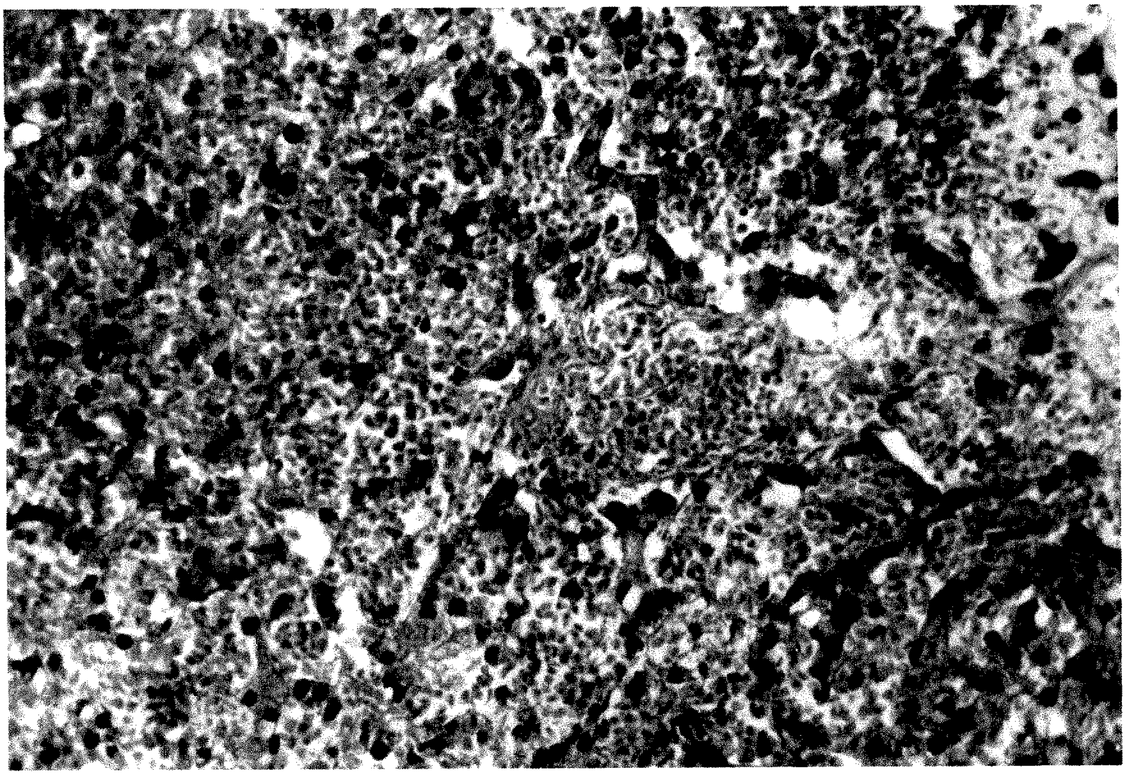

Fig. 5. Case II. Higher magnification of central zone of Figure 4 illustrating central hepatic cord atrophy and extreme sinusoidal congestion with erythrocytes, typical of acute radiation hepatitis (H&E×500).

at less than 60 days following completion of radiation therapy revealed a typical histologic pattern (Fig. 4 and 5). In these specimens the general lobular architecture was intact. The portal spaces and periportal liver cells were normal. There was no effect on the bile ducts. The periportal arteries and veins were normal in appearance. The dramatic findings were located in the centrolobular region. These consisted of severe sinusoidal congestion, hyperemia or hemorrhage, some atrophy of the central hepatic cells, and mild dilatation of the central veins with erythrocytes. No thrombi were found. The central hepatocytes may be atrophic, but exhibited no karyorrhexis or karyolysis. No mononuclear cell infiltrate was present. Scattered fat vacuoles were found in the hepatic cells of the hyperemic areas.

All of these abnormalities, observed at less than 60 days following completion of treatment, represent what we consider the acute effects of radiation. Another smaller group of specimens, obtained either by biopsy more than 100 days post irradiation or at autopsy showed a less distinct pattern, which we believe constitutes the chronic or late effect of radiation upon the liver.

These late changes are extremely variable. They may be only minimal, as in Case II (Fig. 6), which 10 months post irradiation and 9½ months after Figures 4 and 5, showed a normal architectural pattern of the liver cells, normal portal spaces and no areas of abnormal scarring. There was no sinusoidal congestion or hemorrhage; the central veins were normal in appearance. Occasionally, these were areas in which the hepatic cells appeared to be replaced by large fatty vacuolated cells. More often, the late changes showed atrophy of the centrolobular hepatic cords, minimal erythrocyte distention of the sinusoids, and thickening of the central vein wall, varying from only hyaline thickening of the endothelium to complete occlusion of the vein. The periportal areas appeared little changed. The above changes will be further described and elucidated in a forthcoming publication by one of the authors (G.R.).

Autopsy on Case III was performed 166 days after completion of radiation therapy and 24 hours post mortem. The appearance of the liver (Fig. 7) did not fit well with the above description. None of the previous severe centrolobular hemorrhage was encountered. No tumor infiltrate was found. The portal triads were normal. The lobular architecture was distorted by an irregular hyperplasia. The shape of the liver cells was more variable than is normal and they were grouped in mosaic patterns. The sinusoids appeared to meander. Few central veins were identified; some were narrowed, but there was no evidence of vein wall thickening.

Histologic specimens from the left lobe of the liver were obtained at less than 60 days after 5,500 rads, and were identical with the picture described above for acute radiation hepatitis. Unfortunately, no histologic material was obtained at longer intervals. We have not been able to correlate the severity of the histologic picture with the dose of localized radiation; *i.e.*, liver biopsies obtained after 3,000 rads, if positive for acute changes, were indistinguishable from those following 5,500 rads. However, we do anticipate that, as our series is expanded, we will obtain biopsies showing a gradation of acute changes.

DISCUSSION

The liver is evidently not a radioresistant structure when irradiated in its entirety. Its radiosensitivity perhaps is only exceeded by that of the bone marrow, lymphoid tissue, germinal tissue, and kidneys. However, limited portions of the liver

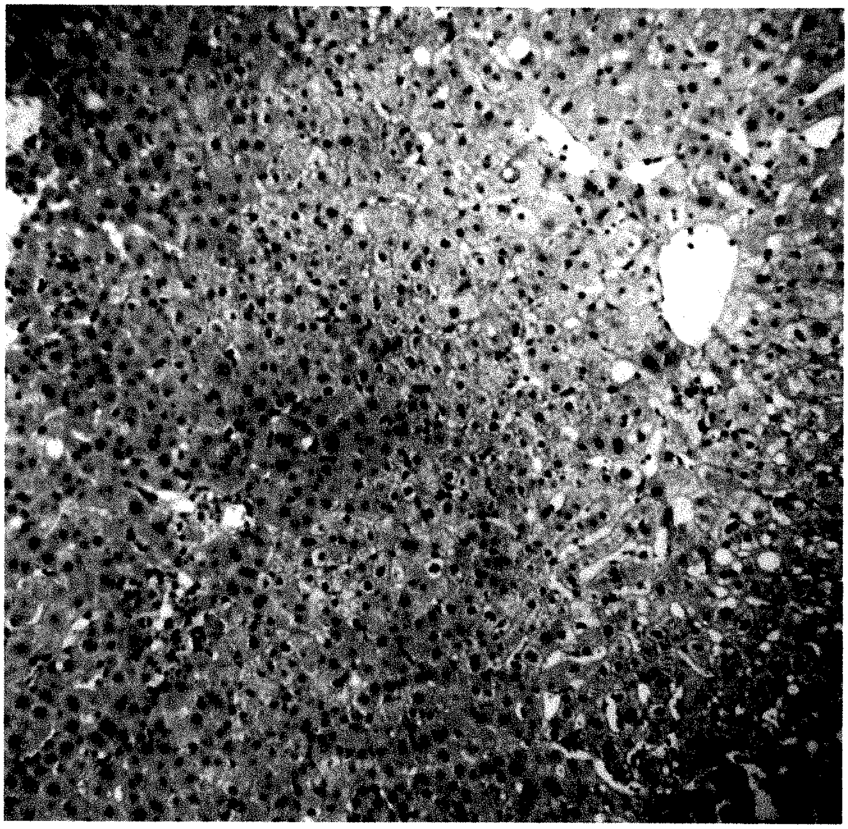

Fig. 6. Needle biopsy of Case II, 10 months post irradiation and 9½ months after the needle biopsy in Figures 4 and 5. Scattered fat vacuoles are seen in the parenchyma; the lobular architecture, the portal spaces, and the central veins are normal (H&E×200).

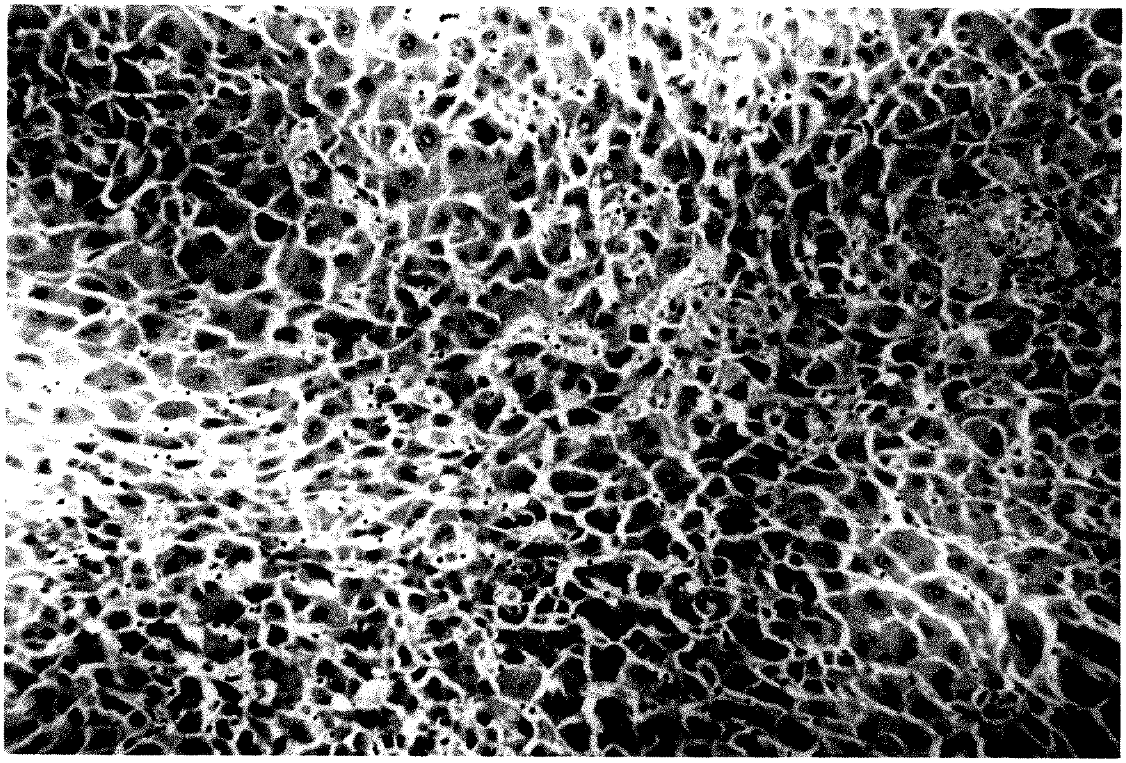

Fig. 7. Microphotograph of autopsy specimen of Case III, 24 hours post mortem and 166 days post irradiation of the entire abdomen, shows irregular hyperplasia, small focal areas of necrosis, and loss of definite portal and central zones. Also noted are bizarre nuclear and cellular shapes. No tumor is seen (H&E×426).

can apparently stand doses as high as 5,500 rads without detectable deleterious effects to the individual.

There has been a variety of responses in our 13 patients with the diagnosis of radiation hepatitis (Table II). Three of the 13 died soon after the completion of therapy due to widespread tumor, and therefore we were unable to evaluate the outcome of their autopsy proven hepatic injury. In none of these cases did the pathologist believe the liver changes to be due to tumor metastases. Three of the 13 died as result of hepatic injury believed secondary to irradiation. Autopsy in each of these cases revealed extensive hepatic injury, and, in 1 of these cases (Case III), needle biopsy had been obtained during the acute phase. In 1 case no tumor was found, and in the other 2, each had a single microscopic focus in a lymph node. Seven of the 13 are still alive at more than 1 year. Two patients have persisting abnormalities of liver function tests and hepatomegaly; both of these patients had diagnostic needle biopsies during the acute phase. The remaining 5 patients have shown complete recovery of liver function tests and their livers are no longer enlarged.

It appears that the safe dose of radiation to the entire liver is in the range of 3,000–3,500 rads, but not exceeding 3,500 rads. Whether this amount of radiation is effective in controlling lymphomas and disseminated ovarian tumors is yet to be clarified.

The treatment of radiation hepatitis is governed by the same principles and modes of therapy used in the medical management of other hepatic insufficiencies, no matter what their cause. An adequate diet with salt restriction and bed rest is essential. Diuretics and paracenteses should be employed as indicated. The place of steroids is not clear, and we have used them in only 1 instance (Case III).

SUMMARY AND CONCLUSION

1. The clinical features of radiation hepatitis, a hitherto unreported complica-

TABLE II

CURRENT STATUS OF PATIENTS WITH DIAGNOSIS OF RADIATION HEPATITIS

Died with extensive tumor before outcome of hepatic injury could be fully evaluated	3/13
Died due to radiation hepatitis (3,850; 4,500; 5,100 rads)	3/13
Alive with persisting evidence of liver damage at more than 1 yr. (3,900; 3,975 rads)	2/13
Alive without persisting evidence of liver damage, *i.e.*, recovery (3,500; 3,950; 4,000; 4,000; 4,200 rads)	5/13

tion of irradiation of the entire liver, have been presented. The principal manifestations are hepatomegaly and ascites, often accompanied by jaundice. There is concomitant deterioration of liver function. The condition may be transient and may require little therapy, or terminate in death due to hepatic insufficiency. The human liver, therefore, should not be regarded as a radioresistant organ.

2. Histologically, the acute effects of radiation are those of centrolobular hemorrhage and sinusoidal congestion with adjacent minimal hepatic cellular atrophy. The late or chronic changes are less distinct, but do show more hepatic cellular damage and changes of the central vein walls.

3. There appears to be a relationship between increasing doses of irradiation and the incidence of liver changes. Doses of 3,000–3,500 rads to the entire liver in 3 to 4 weeks seem relatively safe.

4. The effectiveness of 3,000–3,500 rads to the entire liver in 3 to 4 weeks in controlling lymphomatous liver metastases is yet to be ascertained.

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ACUTE PATHOLOGIC ALTERATIONS IN X-IRRADIATED PRIMATE FETUSES*

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THE histopathologic alterations produced in adult mammals have been extensively studied and are common knowledge.[2,9,12] On the contrary, the information regarding the irradiation injury to the embryo and fetus is rather fragmentary.[4,6,9,12] This is particularly true for the fetuses irradiated *in utero* during late pregnancy. Within the last decade numerous experiments have been performed by one of us (R.R.) in order to determine the effects of controlled exposures of ionizing radiations on the pathogenesis of congenital anomalies in rodent embryos and fetuses irradiated at exact gestation days.[8] A study on the reaction of various organs and tissues of fetal primates to ionizing radiation was subsequently undertaken. The present report refers to histopathologic changes observed in monkey fetuses acutely irradiated *in utero* during the last third of pregnancy.

MATERIAL AND METHODS

Macaca rhesus monkeys, ranging in weight from 5 to 7 kg., were obtained from India by air. When x-irradiated, they were in the fourth or fifth month of a 5 to 5½ month pregnancy. A total of 9 monkeys were x-irradiated for this study (Table 1). Three fetuses of unirradiated monkeys were used as controls.

A single dose of roentgen rays was delivered from a single tube, with rays limited by a 3 inch diameter lead cone. The physical factors were 184 kv. peak, 30 ma., filtration of 0.28 mm. Cu and 0.50 mm. Al, with a half value layer of 0.6 mm. Cu. The air dose to the gravid uterus at 18 cm. distance was 400 r/min., but, figuring a depth dose at 3 cm. (target skin distance was 15 cm.), there was a decrement of 38 per cent so that the dose delivered to the fetus was estimated at 248 r/min. The pregnant monkeys were anesthetized with veterinarian nembutal (0.5 cc./kg. body weight, I.M.) and were tied down on their backs in such a position that the gravid uterus came directly beneath the x-ray beam. It is recognized that the dose to the various regions of the fetus would not be the same, but with fetuses of the range of 140 mm. crown-rump length and 360 gm. body weight, characteristically cramped into the uterus, it is very unlikely that the variation in actual rads absorbed within a single fetus would range more than 20 per cent at the most. Following irradiation, the monkeys were wrapped in adequate burlap to keep them warm and returned to their cages. They were observed for complete recovery, and were given food and water ad libitum.

The fetuses were delivered by cesarean

Table I

Fetus No.	Fetal Dose in r	Fetal Age at Irradiation	Interval between Irradiation and Cesarean Section
6	260	130 da.	19 hr.
5	260	110–120 da.	20 hr.
52	310	125 da.	24 hr.
53	372	115 da.	24 hr.
11	264	160 da.	42 hr.
13	200	130 da.	48 hr.
49	400	110 da.	52 hr.
20	200	135 da.	20 da.*
23	200	110 da.	49 da.*

* Delivered spontaneously at term and sacrificed at 13 days of age.

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Based on work performed under Contract AT(30-1)-2740 for the U. S. Atomic Energy Commission and aided in part by Grant RH-81 from the Division of Radiological Health, Bureau of State Services, U. S. Public Health Service.

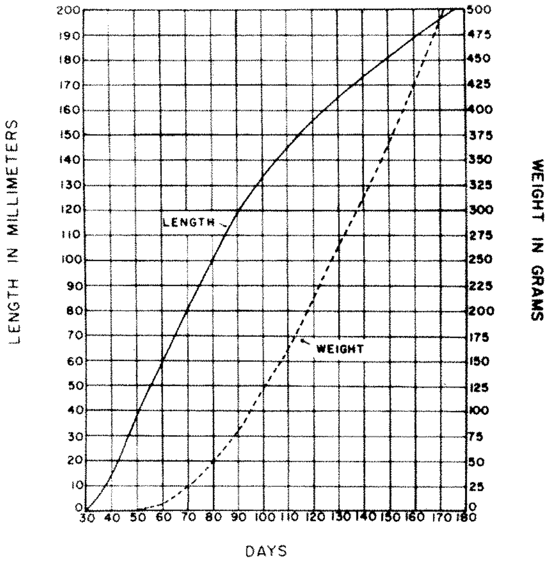


FIG. 1. Curves for calculating monkey fetal age on basis of weight and crown-rump length (after Dr. van Wagenen).

section at various intervals from irradiation (Table 1), and the tissues were fixed immediately. Total body weight and crown-rump length were determined in order to estimate the fetal age using a table compiled by data from Dr. G. van Wagenen (Fig. 1).

A total of 27 organs and tissues of monkey fetus, both control and x-irradiated during the last third of pregnancy, was included in this study. They were the skin, esophagus, stomach, small and large intestine, liver and biliary tract, pancreas, trachea, lung, heart, thymus, kidney, ureter, urinary bladder, spleen, lymph nodes, thyroid, parathyroid, adrenal, ovary, fallopian tubes, uterus, testis, epididymis, sympathetic ganglia, and skeletal muscle. Other tissues and organs, such as central nervous system, eyes, teeth, bones, and bone marrow are being studied by other investigators and will be reported separately.

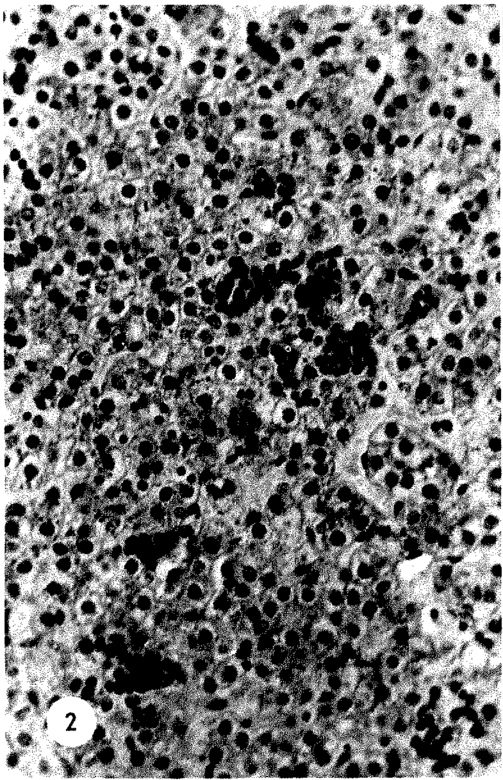
The tissues were fixed in Bouin's fluid and stained with hematoxylin and eosin and with PAS. In addition, some selected sections were stained with Sharlach R and with mucicarmine.

RESULTS

No abortions were caused by the irradiations used, and no gross anomalies could be detected in any of the organs. This was explained by the fact that the irradiation in all cases occurred after the completion of organogenesis when gross congenital anomalies can no longer be induced. Histologically significant changes were seen in liver, kidneys, thymus, spleen, and lymph nodes. The remaining organs of the above list did not show significant histopathologic changes.

The Liver. (Fig. 2–5). The hepatic cells appeared to be very susceptible to irradiation insult. Degenerative changes were seen in livers of all the monkey fetuses sacrificed within 52 hours after the time of irradiation. The degeneration was in the form of large cytoplasmic vacuoles which pushed the nuclei to the periphery of the cells (Fig. 3). The content of the vacuoles stained bright red with Sharlach R and did not stain with PAS

FIG. 2–5. (*2*) Normal liver of rhesus monkey fetus at term showing a focus of hemopoiesis (H&E×240). (*3*) Fatty degeneration and depression of hemopoiesis in liver of rhesus monkey fetus (310 r, 24 hr. interval) (H&E×540). (*4*) Recovery of liver cells and no hemopoiesis in liver of rhesus monkey fetus (200 r, 49 day interval) (H&E×540). (*5*) Subcapsular hemorrhage in fetal liver of rhesus monkey (310 r, 24 hr. interval) (H&E×240).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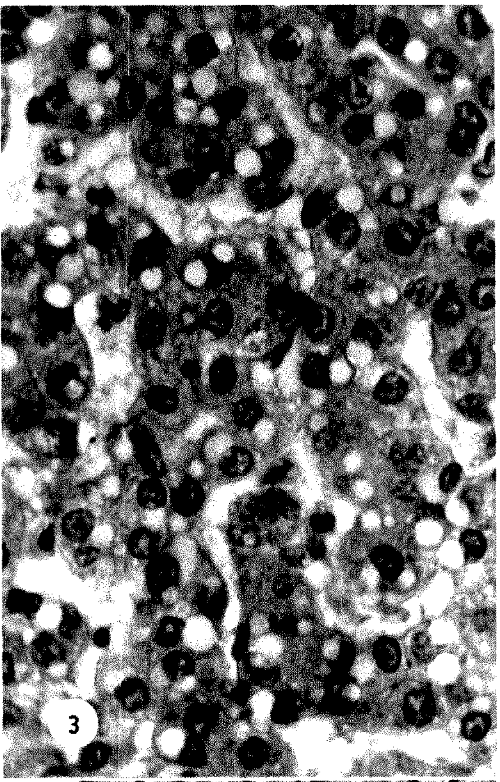
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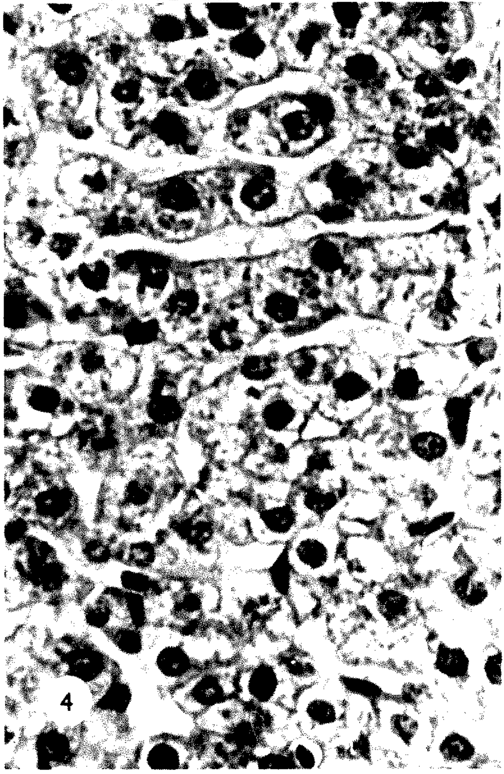
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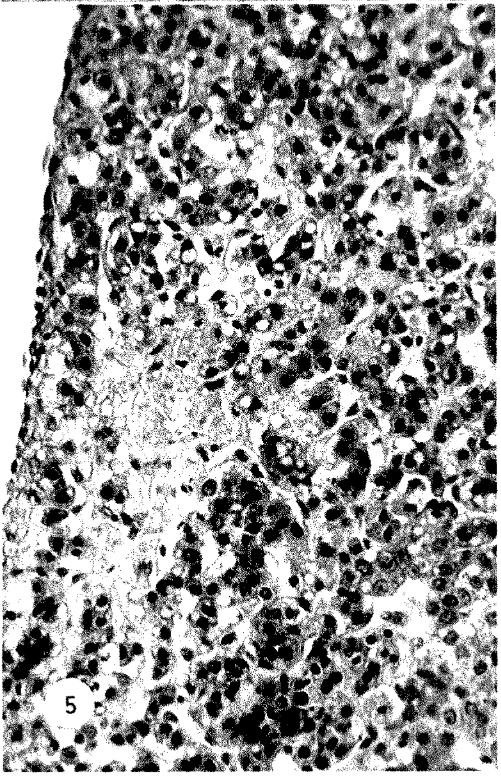
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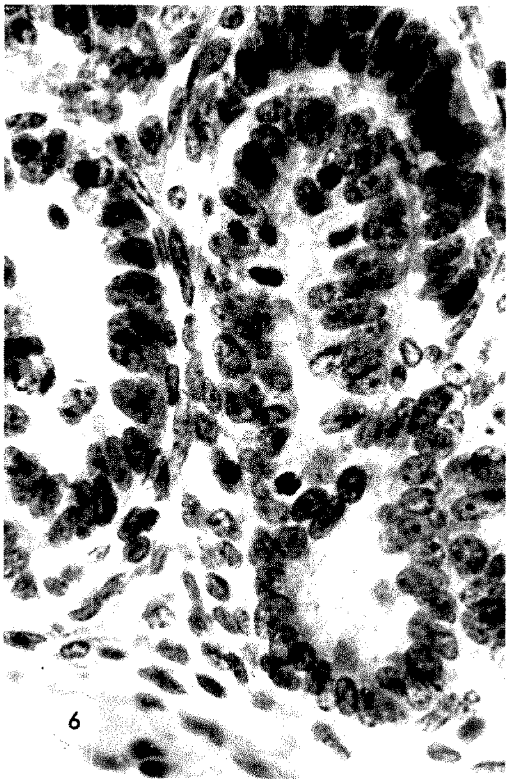

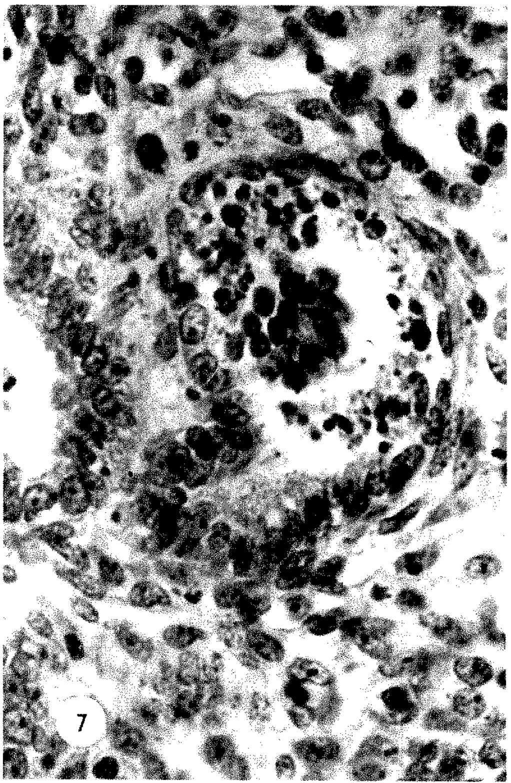

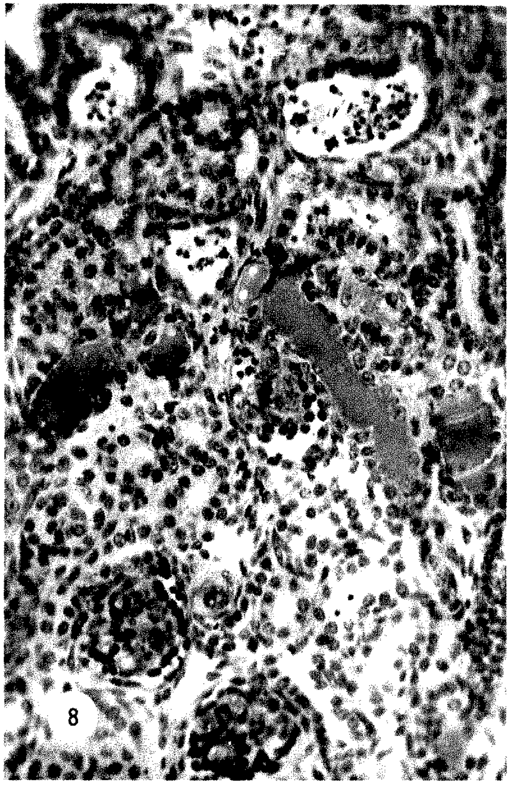

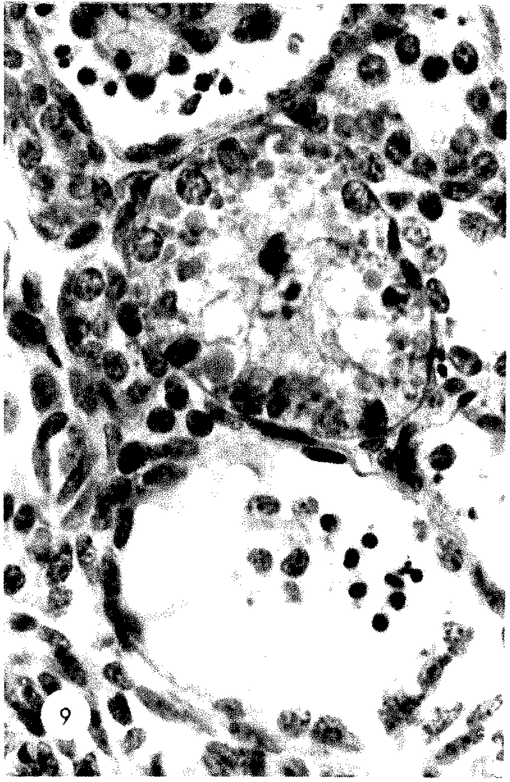

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and mucicarmine, thus indicating its lipid nature. The fatty degeneration involved the liver parenchyma in a diffuse manner without predilection for any particular portion of the lobules. The monkey fetuses sacrificed within 24 hours of irradiation showed from mild to moderate fatty degeneration after 260 r and 310 r, and marked degeneration after a dose of 372 r. The degeneration appeared to be worse in those fetuses sacrificed between 42 and 52 hours after irradiation. By 20 days following exposure, the liver cells appeared to have completely recovered. Extramedullary hemopoiesis was generally depressed (Fig. 3) and this depression ranged from mild, in the monkeys exposed to 260 r and sacrificed in 19–20 hours, to marked, in the monkeys exposed to 310 r or 372 r and killed 24 hours later. Fetus 11 showed total obliteration of hepatic hemopoiesis 42 hours after receiving 264 r. Only scattered nucleated red blood cells were seen in the liver of fetuses 13 and 49 which were exposed to 200 r and 400 r and were sacrificed after 48 and 52 hours, respectively. The depression of extramedullary hemopoiesis involved all elements, but the nucleated red blood cells proved to resist the insult longer. It is interesting to note that the gradual disappearance of the foci was not accompanied by an equivalent accumulation of necrotic debris. The depression of extramedullary hemopoiesis appeared to be long-lasting since in the liver of the monkeys sacrificed after 20 and 49 days (Fig. 4) only occasional nucleated red blood cells could be seen. These cells did not necessarily represent extramedullary hemopoiesis since they appeared to be in the circulating blood. The depression of extramedullary hemopoiesis was accompanied by a marked decrease in the number of mitoses in the remaining cells.

In 3 fetuses which received 310 r, 372 r, and 400 r, and were sacrificed 24, 24, and 52 hours thereafter, megakaryocytes were more numerous and more prominent than in the controls.

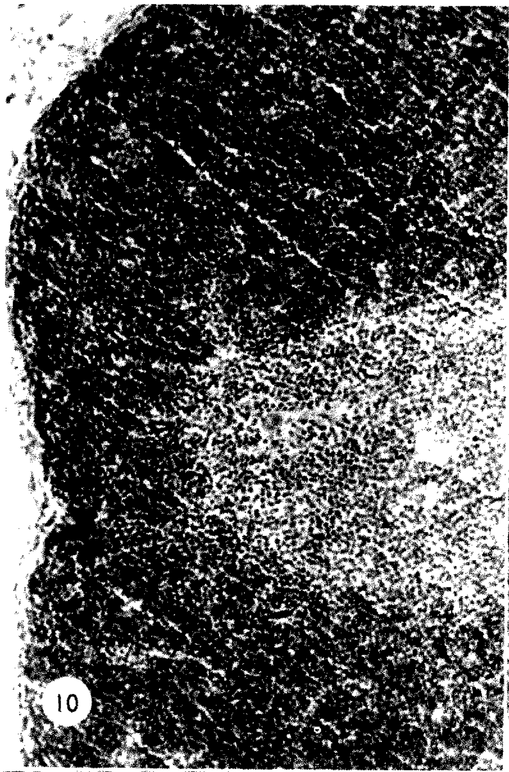
In only one monkey fetus (dose of 310 r and sacrificed at 24 hours) was there evidence of small subcapsular hemorrhages with some destruction of the liver cells in the hemorrhagic foci (Fig. 5). The other irradiated monkeys simply showed some subcapsular congestion or no vascular changes. No vascular alterations were detectable in the livers of the control fetuses. To what extent these vascular changes are related to the irradiation is therefore debatable. It is possible that the condition is at least in part related to operative trauma at the time of cesarean section.

No increase in phagocytosis and no fibrosis could be seen in any of the cases. Mitotic figures among the control and experimental fetal livers appeared to be very few in number so that their evaluation was difficult.

Biliary epithelium, including that lining the gallbladder, did not seem to suffer.

Kidney. (Fig. 6–9). The most striking changes in the kidneys involved the nephrogenic zone. Many developing glomeruli

Fig. 6–9. (*6*) Nephrogenic zone in normal kidney of rhesus monkey fetus at term. Note numerous mitoses (H&E×540). (*7*) Necrosis in nephrogenic zone of kidney of rhesus monkey fetus (372 r, 24 hr. interval). No mitoses (H&E×540). (*8*) Protein-like material in tubules at junction of nephrogenic zone and cortex proper of kidney of rhesus monkey fetus (372 r, 24 hr. interval) (H&E×240). (*9*) Hyaline degeneration of tubular epithelium of kidney of rhesus monkey fetus (400 r, 50 hr. interval) (H&E×540).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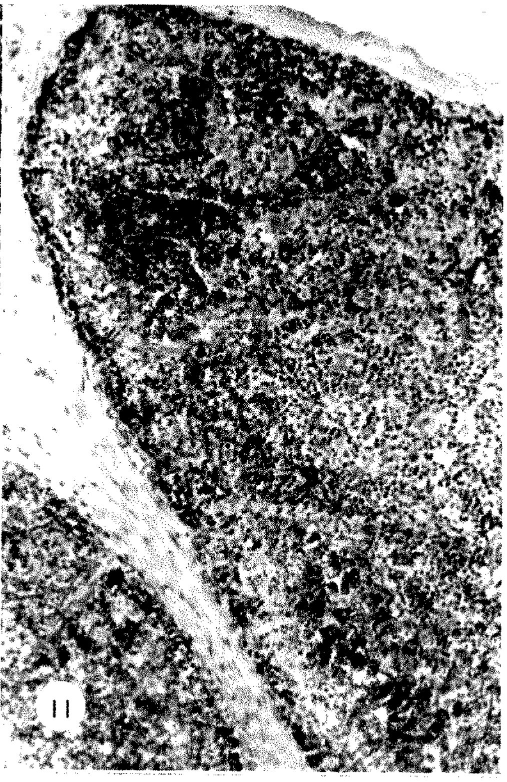
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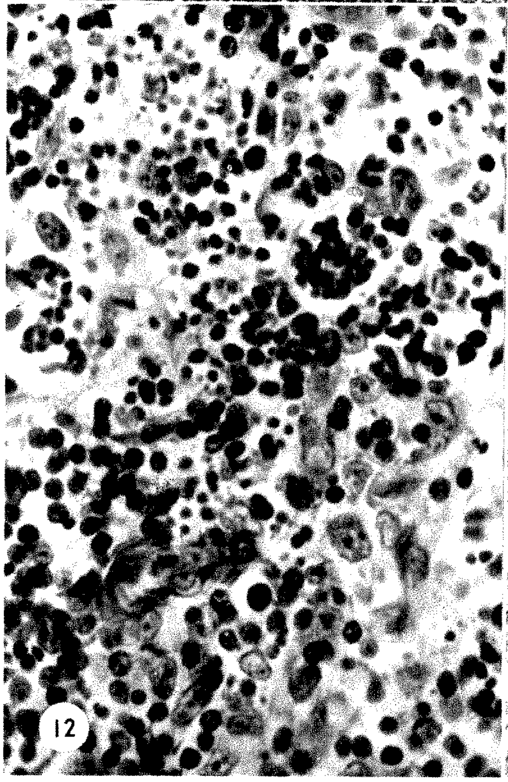
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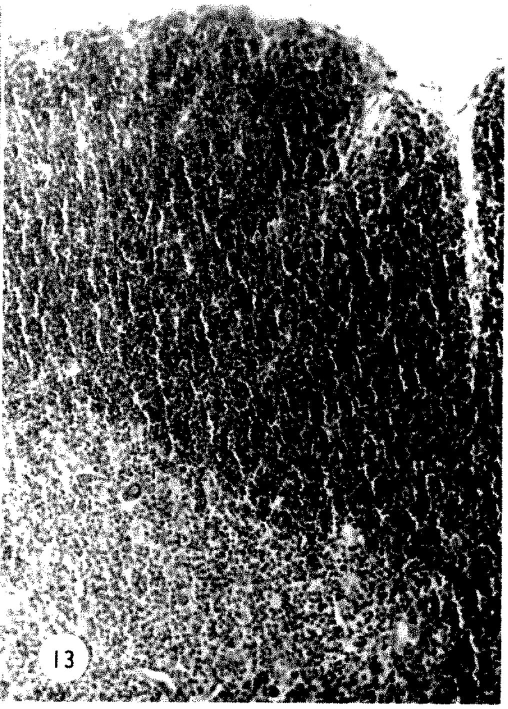
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showed areas of necrosis (Fig. 7) involving the epithelial cells of the future glomerular tufts and proximal convoluted tubules. The space in Bowman's capsule appeared to be distended and contained some fluid and necrotic debris. The amount of debris, however, did not appear to be commensurate to the amount of necrosis and was usually greater than expected. Mitotic figures in the developing nephrons were greatly reduced in number. While in the controls we counted 31 mitoses per 10 high power fields, in the kidney of the irradiated fetuses the number of mitoses ranged from 0 to 5 per 10 high power fields. In the nephrogenic zone there was also a mild to moderate infiltration with polymorphonuclear leukocytes. Such leukocytic infiltration was diffuse with focal concentration and was not necessarily related to the areas of necrosis. These changes were noted in all the fetuses sacrificed within 24 hours of irradiation and in one sacrificed 52 hours after exposure. The animals sacrificed after 42 and 48 hours and those which were kept for 20 days or longer were devoid of the nephrogenic zone altogether.

Some of the tubules at the junction between the nephrogenic zone and the cortex proper showed distention by eosinophilic fluid (protein?) which occasionally appeared so dense as to suggest the possibility of the formation of hyaline casts (Fig. 8). In the fetuses sacrificed late (20 and 49 days postirradiation), some of the subcapsular tubules appeared to be greatly distended and possibly represented microscopic cortical cysts. In one fetus sacrificed after 52 hours, some of the tubules in this same location showed marked hyaline degeneration (Fig. 9). A mild degree of hyaline degeneration was also noted in a fetus sacrificed 24 hours after being exposed to 372 r.

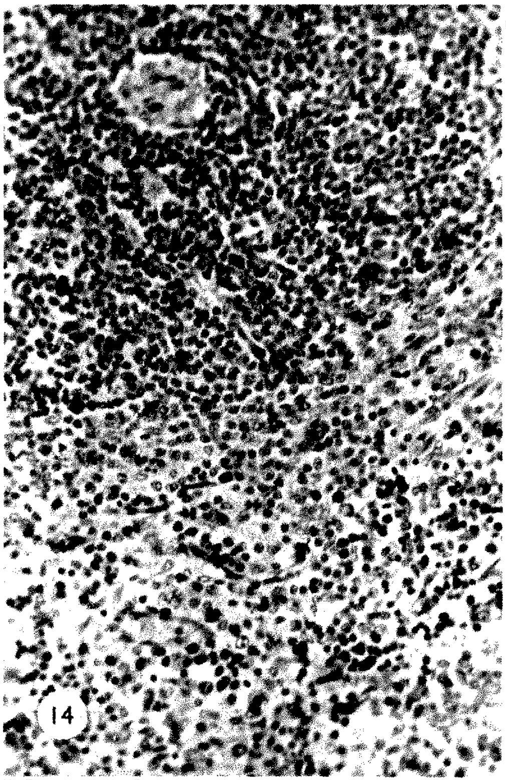
No significant changes could be seen in the cortex proper nor in the medulla.

Thymus. (Fig. 10–13). All fetuses sacrificed between 24 and 52 hours after exposure showed extensive necrosis of lymphoid cells (Fig. 11) manifested by pyknosis and accumulation of much nuclear and cytoplasmic debris (Fig. 12). In the fetus sacrificed 49 days after irradiation, the distribution and amount of cortical lymphoid tissue returned to normal (Fig. 13).

Mitotic activity was markedly depressed in both cortex and medulla after 24 and 52 hours. However, after 49 days the mitotic activity appeared to be greatly increased, especially in the cortex where the number of mitoses seemed to be even greater than in the unirradiated controls.

In the medulla few foci of necrosis were seen in one case which received 372 r and was sacrificed after 24 hours. With the exception of this one case and of the original depression in mitotic activity, the medullary epithelium did not seem to suffer. Some cystic Hassall's bodies were seen after 49 days and were interpreted as involutionary changes similar to those seen in lymphocyte-depleted thymuses of unirradiated human newborns[10] rather than the result of radiation injury to the medullary epithe-

FIG. 10–13. (*10*) Normal thymus of rhesus monkey fetus at term (H&E×120). (*11*) Destruction of lymphocytes in thymus of rhesus monkey fetus (310 r, 24 hr. interval) (H&E×120). (*12*) Higher magnification of Figure 10. Note the necrosis and nuclear pyknosis of lymphocytes (H&E×540). (*13*) Recovery of lymphocytes in thymus of rhesus monkey fetus (200 r, 49 day interval) (H&E×120).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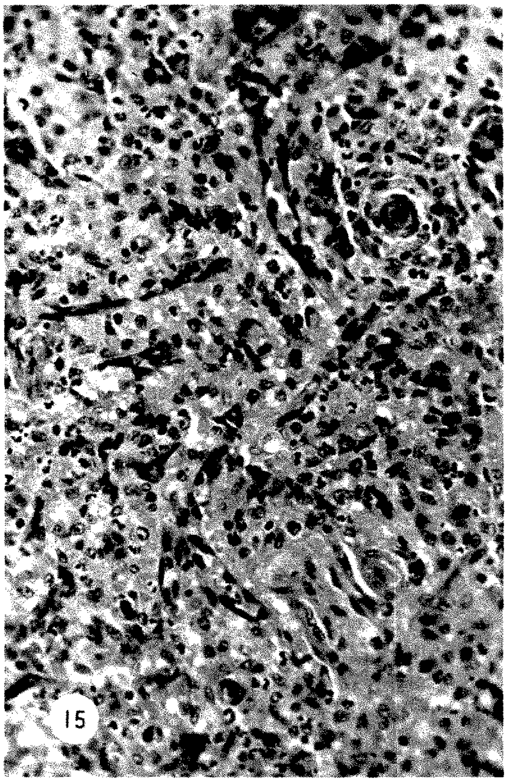
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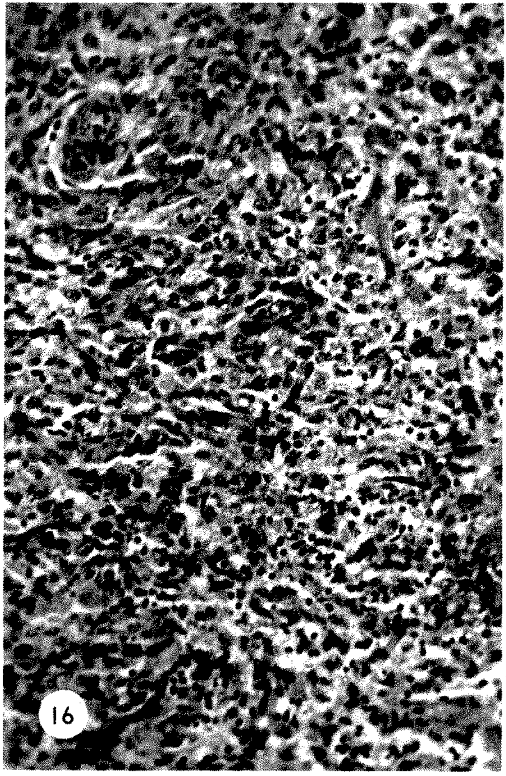
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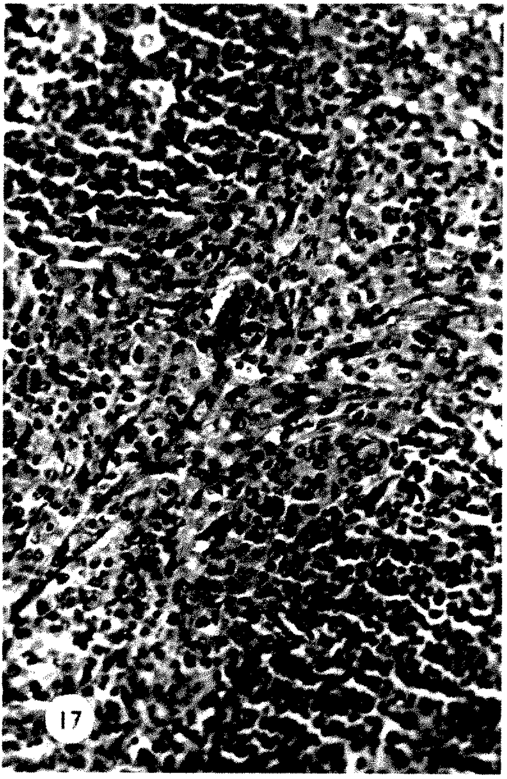
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lium. However, it should be pointed out that no cystic Hassall's bodies were seen in the unirradiated control fetuses used in this study.

Spleen. (Fig. 14–17). Also in the spleen the lymphocytes decreased in number in both white and red pulp. This decrease in number of lymphocytes was not accompanied by noticeable accumulation of necrotic debris and, as a result of it, the white pulp appeared to shrink, leaving the central arteries barren and surrounded by concentrically oriented collagen fibers and making the red pulp more prominent (Fig. 15). The effects on lymphocytes were well demonstrable after 24 hours, but became severe by the second day after irradiation. The fetus sacrificed after 20 days showed a severely depleted white pulp (Fig. 16), while that sacrificed 49 days later disclosed an apparently normal lymphocytic population (Fig. 17).

The reticulum cells of the red pulp seemed to be more prominent in all of the cases, but this was probably the effect of the decrease in lymphocytes. Among the reticulum cells, megakaryocytes were occasionally seen and in one case they were probably more numerous than expected.

The number of mitoses was greatly decreased in all cases, especially in the white pulp.

As in the liver, the extramedullary hemopoiesis suffered a marked depression, the more primitive cells being the more severely affected. All cases showed a marked depression of approximately the same magnitude (Fig. 15 and 16) with the exception of the fetus sacrificed after 49 days in whose spleen no traces of hemopoiesis could be found (Fig. 17).

The congestion in the red pulp was from mild to moderate in the fetuses sacrificed within 50 hours and was questionable in those allowed to survive for 3 or more weeks. Subcapsular hemorrhages were seen focally only in one case which received 260 r and was sacrificed after 20 hours.

Most of the cases showed diffuse infiltration with polymorphonuclear leukocytes (Fig. 15) ranging from mild to moderate in severity. No obvious increase in phagocytosis was seen. Similar alterations were observed in accessory spleens.

Lymph Nodes. (Fig. 18–21). Severe loss of small lymphocytes was an outstanding feature in all cases sacrificed within 50 hours of irradiation (Fig. 19). The loss of lymphocytes was accompanied by a small amount of debris, some infiltration with polymorphonuclear leukocytes and by the appearance of occasional megakaryocytes. The reticulum cells did not appear to be affected although they appeared to be more prominent as the lymphocytes disappeared. The number of lymphocytes returned to normal in the fetus sacrificed after 49 days (Fig. 21). On the contrary, the fetus sacrificed after 20 days showed marked depletion of lymphocytes (Fig. 20). It is interesting to note that the latter fetus (fetus No. 20) showed also lymphocytic depletion of the

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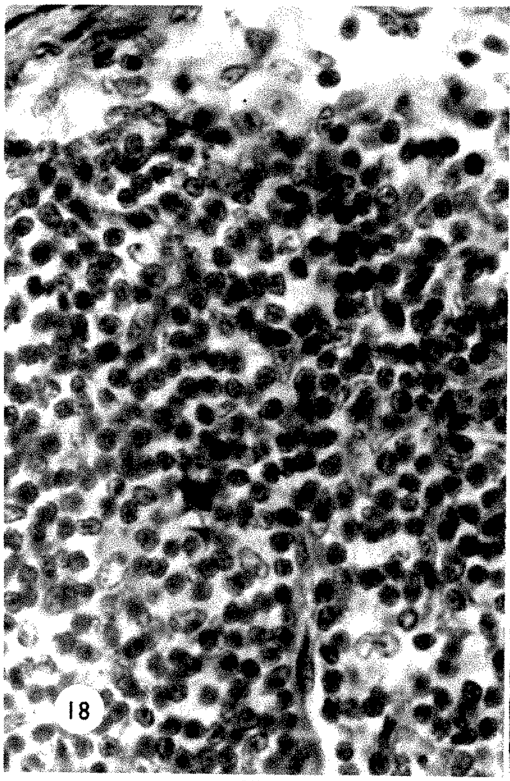
Fig. 14–17. (*14*) Normal spleen of rhesus monkey fetus at term. Note hemopoiesis in red pulp (H&E×240) (*15*) Loss of lymphocytes with obliteration of white pulp in spleen of rhesus monkey fetus. Marked depression of hemopoiesis (264 r, 42 hr. interval) (H&E×240). (*16*) Absence of lymphocytes in spleen of rhesus monkey fetus. Persistent depression of hemopoiesis (200 r, 20 day interval) (H&E×240). (*17*) Recovery of white pulp in spleen of rhesus monkey fetus (200 r, 49 day interval). No hemopoiesis (H&E×240).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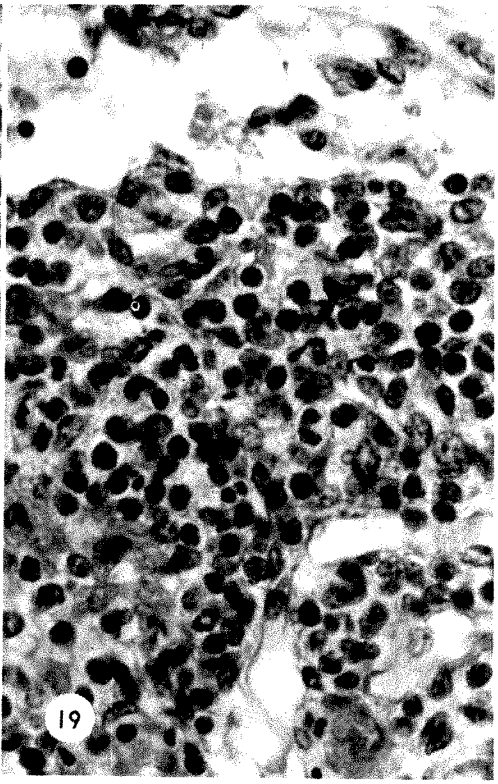
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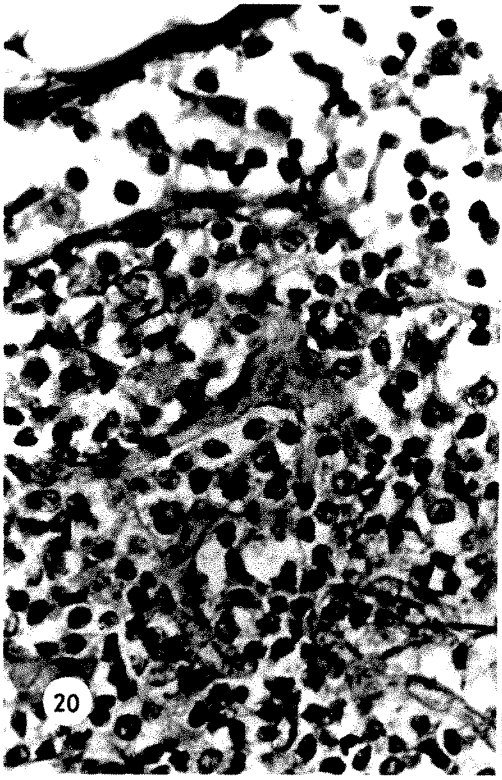
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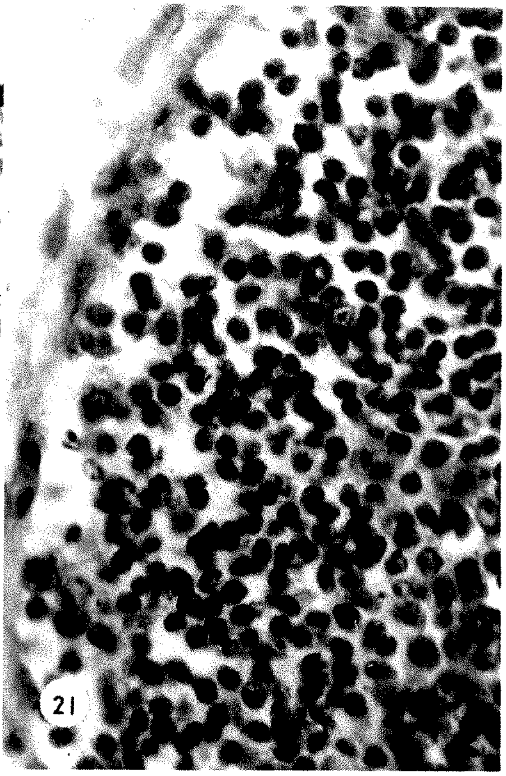
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white pulp of the spleen, while the fetus sacrificed after 49 days showed good recovery in the number of lymphocytes in spleen, lymph nodes and thymus. Unfortunately, the thymus of fetus No. 20 was not available.

Mitoses were very infrequently seen in the lymph nodes of fetuses sacrificed in the first 50 hours after irradiation. However, it is difficult to estimate accurately the effect on the mitotic activity in the postirradiation period since the controls also showed few mitotic figures. On the other hand, in the fetuses sacrificed late, the lymph nodes showed a considerable increase in mitotic activity similar to that seen in the cortex of the thymus.

No germinal centers were seen in the animals sacrificed before birth. In those allowed to survive for 3–5 weeks, only a few early germinal centers were seen.

DISCUSSION

A few points deserve further comment. From the foregoing description, it is apparent that the *acute* stages of reaction to x-ray insult (200 to 400 r) in monkey fetuses in the last third of gestation are characterized be degeneration and/or necrosis of sensitive cells and depression of mitotic activity. Some of the resulting lesions are reversible while others are permanent.

The fatty degeneration of the liver cells is quite extensive in the acute phase, but in spite of its severity it is followed by a complete recovery as judged by the morphologic observations made with the light microscope. However, morphologic recovery does not necessarily mean functional recovery and one wonders what is the fate of various enzymatic systems under these circumstances. Similar considerations can be made about the apparently unaffected nephrons. The necrosis of the nephrons in the nephrogenic zone is rather striking especially when confronted with the radioresistance of the nephrons that have reached maturity. Nevertheless, this is not surprising and supports the time-honored rule that younger cells are more readily injured by irradiation. What damage, if any, follows the acute injury on the nephrogenic zone is difficult to evaluate on account of the limited number of cases available. However, with this limitation in mind, we feel that possibly the necrosis and the loss of mitotic activity observed in the first two postirradiation days may result in a premature disappearance of the nephrogenic zone. It is also possible that the distention of the tubules at the junction between the nephrogenic zone and the cortex proper seen in the early stages leads to the formation of microscopic cortical cysts.

The damage to the lymphoid structures is expected. It is of interest to observe that this damage varies in type and extent from organ to organ. In the first 2 days after irradiation, while the thymus displays the severest loss of lymphocytes due to necrosis of the lymphocytes themselves with great accumulation of necrotic debris, the lymphocytes in the lymph nodes and spleen decrease in number but without proportionate

FIG. 18–21. (*18*) Normal retroperitoneal lymph node of rhesus monkey fetus (20th week of pregnancy) (H&E×540). (*19*) Loss of lymphocytes in retroperitoneal lymph node of rhesus monkey fetus (372 r, 24 hr. interval) (H&E×540). (*20*) Depletion of lymphocytes in retroperitoneal lymph node of rhesus monkey fetus (200 r, 20 day interval) (H&E×540). (*21*) Recovery of lymphocytes in axillary lymph node of rhesus monkey fetus (200 r, 49 day interval) (H&E×540).

necrosis of the cells. One gains the impression that the lymphocytes of the thymus are more directly and readily affected by irradiation. This lends support to the observation that the lymphocytes of different organs differ from each other.[1,3,6,7] The loss of lymphocytes appears to be temporary and reversible, but it is possible that it might be quite long-lasting or might become permanent in some cases as judged by the depletion of lymphocytes in the spleen and lymph nodes of the fetus sacrificed 20 days after exposure.

The effects on extramedullary hemopoiesis appear to be irreversible or of particularly long duration. In both liver and spleen, hemopoiesis is severely depressed in the early phases and it eventually disappears altogether. But this rapid loss of hemopoiesis is not accompanied by accumulation of necrotic debris as one would expect, raising the question as to where the cells go. Unquestionably the depression of hemopoiesis is largely accounted for by the loss of mitotic activity and actual destruction of cells. However, one wonders as to whether some of the cells might be "called" prematurely into the circulation as a response to the decreased formation of cells in the bone marrow and in the extramedullary foci.

The ability of cells to undergo mitotic division is greatly impaired in the nephrogenic zone, lymphoid tissue, and in foci of extramedullary hemopoiesis during the first postirradiation days. However, in the lymphoid tissue, when capable of complete recovery, the mitotic activity returns to normal and may even become greater than normal during the process of regeneration.

Unexpectedly, certain organs which are commonly believed to be radiosensitive (*e.g.*, the mucous membrane of the small intestine and the gonads) did not show any appreciable alteration in either the early or late postirradiation phases. Adult rabbits exposed to 400 r x-rays showed pathologic changes in the gastrointestinal tracts beginning 1 hour following exposure and persisting for 5 days thereafter.[2] In this connection, it is interesting to note that we did not detect any histopathologic changes even in the small intestine of a younger primate fetus exposed to 400 r at 82 days of intrauterine life and sacrificed 3¾ hours afterwards.

SUMMARY

Pathologic alterations were studied in various organs and tissues of monkey fetuses which had received x-irradiation *in utero* (200 r to 400 r) during the last third of pregnancy. The following major alterations were observed:

1. Fatty degeneration of liver cells during the first 2 days after exposure, followed by complete recovery.
2. Necrosis of epithelial cells in the nephrogenic zone of the kidney leading to premature disappearance of this zone.
3. Severe necrosis of lymphocytes in the thymus and depletion of lymphocytes in spleen and lymph nodes. The lymphocytic population of these organs may or may not return to normal in a period of 3 weeks or longer following exposure.
4. Marked depression of extramedullary hemopoiesis in liver and spleen, sometimes followed by partial recovery.
5. Marked depression of mitotic activity.
6. Unexpectedly, no severe histopathologic alterations were detected in the intestinal tract or in the gonads.

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NEW OBSERVATIONS CONCERNING ROENTGEN SENSITIVITY OF PIGMENT CELLS IN YOUNG AXOLOTLS (Siredon mexicanum)*

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THE pigment cells of axolotls (melanophores—the main type, containing the black pigment granules of melanin and xanthophores with yellow and green pigment—lipochrome) are distributed not only in the subepithelial layer of loose connective tissue, but also in some of the internal organs, such as the spleen and especially the liver. Investigations have shown much diversity in the reaction of melanophores to irradiation. In many cases the irradiated portion of the body (*e.g.*, the tails of young axolotls[6]) loses its pigmentation and becomes light and transparent. The pigment layer is destroyed and the majority of the melanophores are transformed into globular forms without processes. The number of pigment cells is greatly reduced.[2,3,4,5,6,39] According to Brunst and co-workers,[20] "The general condition of the pigment layer in the treated region differs greatly from that in the control animals. One of the most permanent signs of the primary acute reaction to irradiation is the degeneration of the pigment layer caused by a decrease in the number of pigment cells and changes in their shape. Instead of showing their typical form with numerous processes, they become globular. The first sign of an irradiation effect is the presence of degenerated pigment cells. In some cases these cells were observed, not only during the primary acute reaction to irradiation, but some time after this period. In some areas of the treated region, the pigment cells completely disappeared; in other places, an accumulation of degenerated pigment cells was observed. However, in some parts of the treated tissues it is possible to observe normal pigment cells." On the other hand, the reduction of pigment layer was not observed after irradiation of the lower jaws of young axolotls[21] nor after irradiation of various portions of the bodies of young axolotls.[8,11] In a new investigation of the successive changes in the skin epithelium of the head of the young axolotl[18] after irradiation, the reduction in the number of pigment cells and the formation of globular melanophores without processes were not observed. On the contrary, the melanophores beneath the epithelium and especially the intraepithelial melanophores developed more often than those in normal epithelium. The disappearance of the melanophore processes was not observed, and in some cases these processes were especially large and long. The accumulation of pigment granules in the cytoplasm of the epithelial cells, which could be observed in normal epithelium only in very rare cases, was observed very often and in large quantity after irradiation.

This great difference in the reaction of pigment cells to irradiation may be due to the variation in the radiation condition, doses, and age differences of the experimental animals or to the variable radiosensitivity of melanophores in different portions of the body. The purpose of the present study was to investigate this problem; therefore, identical irradiation was delivered to the tail and head of experimental animals of the same age taken from the same spawning and the reaction of melanophores was compared.

MATERIAL AND METHOD

For this investigation, 175 axolotls from

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one spawning were divided into 7 groups. In 3 groups of animals 24 days after hatching, the anterior portions of the heads were irradiated with 500, 1,500 and 3,000 r, respectively; in another 3 groups, the tails were irradiated on the same day with the same doses; and one group served as untreated controls. The factors of irradiation were as follows: 100 kv., 0.25 mm. Al filter, beryllium window tube; half value layer 0.55 mm. Al; intensity 460 r/min. in air; target object distance 15 cm. During irradiation the animals were placed on a piece of cardboard covered with waxed paper and several layers of moistened filter paper and anesthetized, using a weak aqueous solution of tricaine methanesulfonate (MS-222). The nonirradiated portions were shielded with a lead covering (made from a 4 mm. lead sheet) with a round radiation localizer 6.5 cm. in diameter.[7] The animals were arranged in radial positions during irradiation. They were put into water immediately after treatment, to recover from the anesthesia. Following irradiation, 2 animals were sacrificed and fixed every week. All dying animals were fixed before death occurred.

For histologic study, animals were fixed in acetic mercuric chloride formalin (Stieve). The material was embedded in paraffin with 5 per cent beeswax and sectioned at 8 μ. The sections were stained with Ehrlich's hematoxylin and eosin and in almost all cases photomicrographs were made with the same magnification (× 100). In some cases photomicrographs were made with higher magnification (× 510).

RESULTS

NORMAL MELANOPHORES IN CONTROL ANIMALS

The melanophores even in normal control animals were found to vary greatly. The fact should be considered that young animals a few days after hatching have a very limited number of melanophores, most of which are intraepithelial. Even in animals 24 days after hatching (the day all animals were irradiated), most of the melanophores were intraepithelial and the number was not large. During development, the number of melanophores gradually increased and most new melanophores developed beneath epithelium. This is the beginning of the formation of the underepithelial pigment layer which is typical for older animals, especially adults. In such a layer, so many melanophores are located in close contact that it is impossible to distinguish separate pigment cells. In our material, the development of melanophores in young animals was studied; therefore, formation of a real pigment layer was observed only in very rare cases (Plate v, Fig. 20). In almost all control animals, only well separated branching melanophores were seen beneath the epithelium. For example, the most that could be seen 101 days after hatching was several rows of melanophores, generally well separated (Plate I, Fig. 1 and 2). It is important, however, to take into consideration the variations in the development of melanophores. Even in the same animals, which demonstrated good normal development for their age (Plate I, Fig. 1 and 2), there were few melanophores or none at all in some areas. Normally, such areas are small and seldom observed.

This great variation in the appearance of melanophores is significant. Pernitzsch[35] in 1913 distinguished 2 types of melanophores in the axolotl: a type with many multibranched outgrowths and a type with a few sparsely branched outgrowths. However, he also described many intermediate forms. Variations in, and the condition of, the melanophores depended to some degree upon outside factors, especially light. According to our observations, it is possible to find any type of melanophores in normal animals, including those with very small contracted outgrowths and, in very rare cases, the globular melanophores without any processes.

MELANOPHORES IN IRRADIATED TAILS

A significant difference was observed by comparing the melanophores of control animals with those in irradiated tails. It was

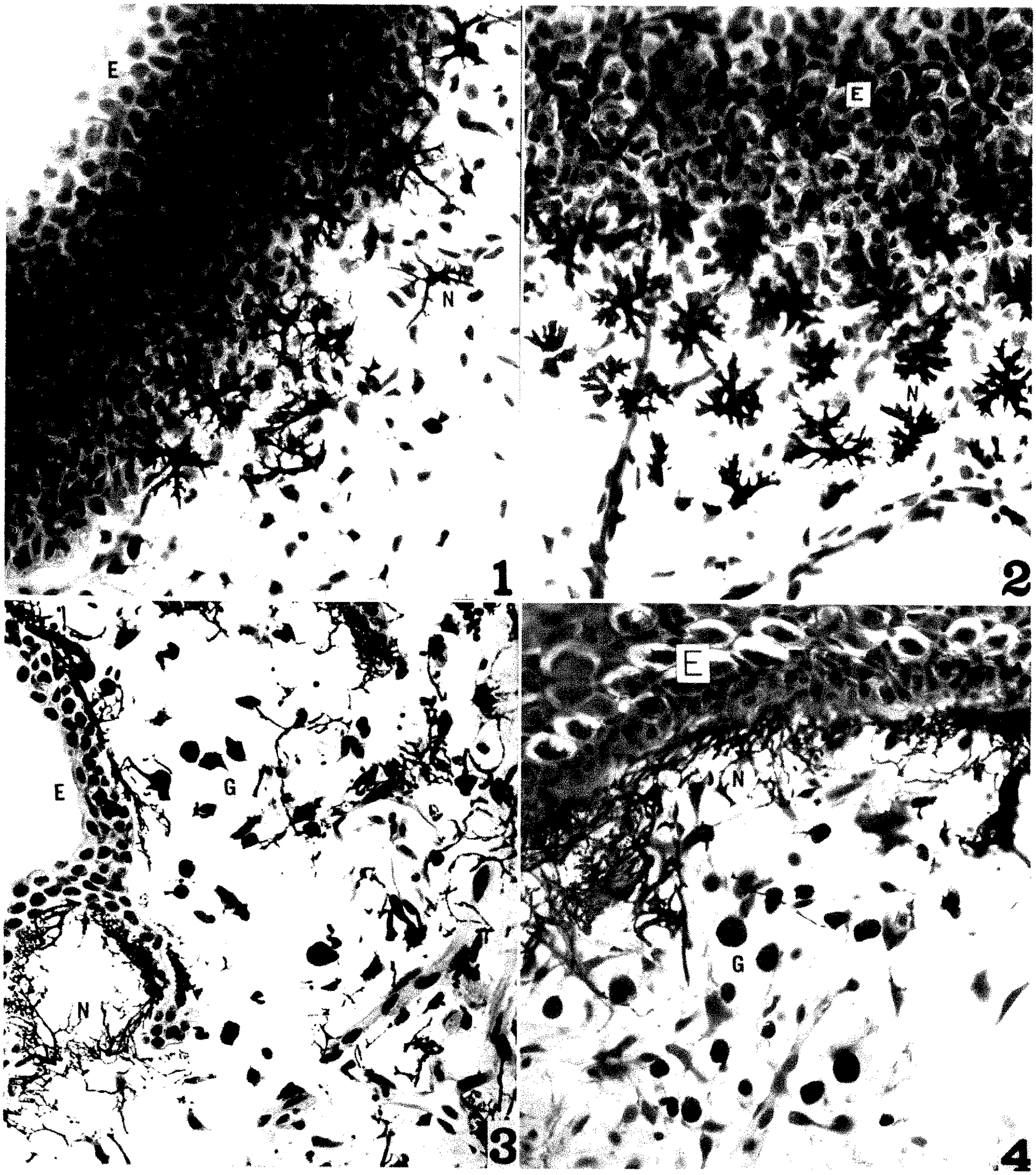


PLATE I

FIG. 1 and 2. Various portions of sections through the tail of control animal 101 days after hatching. (E) Skin epithelium; (N) typical normal melanophores. Photomicrographs, ×100. FIG. 3. Part of the section through the tail of animal fixed 63 days after irradiation with 3,000 r and 87 days after hatching. (E) Skin epithelium; (G) globular melanophores; (N) normal melanophores. Photomicrograph, ×100. FIG. 4. Part of the section through the tail of animal fixed 63 days after irradiation with 1,500 r and 87 days after hatching. (E) Skin epithelium; (G) globular melanophores; (N) normal melanophores. Photomicrograph, ×100.

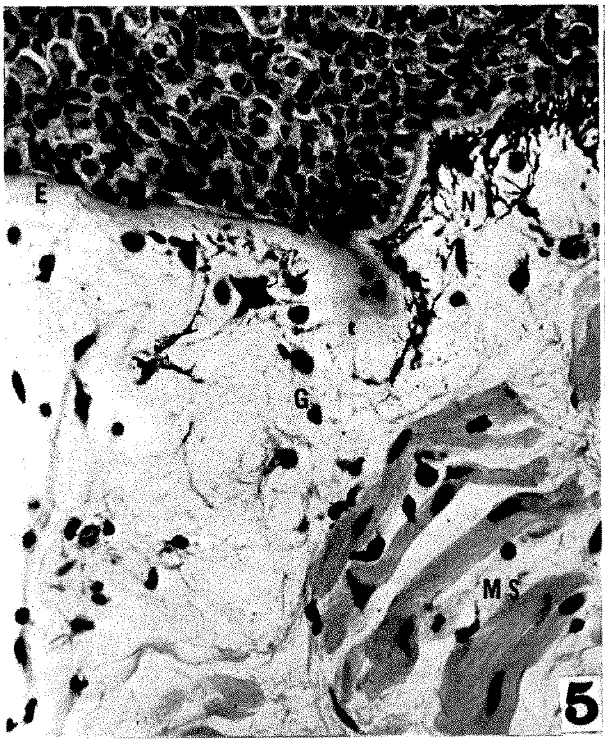
possible to find isolated areas which were identical in irradiated and control animals, but this was the result of individual variations in reaction to irradiation and the discontinuous character of radiation energy.[48] In most areas, however, the result of irradiation was evident. Plate I, Figure 3 shows the typical appearance of melanophores in the tail after irradiation with 3,000 r. In this case the number of melanophores was only slightly reduced, but almost all pigment cells were abnormal. They had a globular or irregular form without any processes. Only in some areas could the long multibranched outgrowths be seen. In other cases, the underepithelial melanophores were only partly damaged (Plate I, Fig. 4), but in all cases the more deeply located cells were globular. At times, after irradiation with 3,000 r (Plate II, Fig. 6 and 8), 1,500 r (Plate II, Fig. 5 and 7; and Plate III, Fig. 10) and 500 r (Plate III, Fig. 11 and 13), the number of melanophores was definitely reduced. This phenomenon was independent of the radiation dose and has been observed after irradiation with the smallest dose even more clearly (Plate III, 11 and 13). In some regions the melanophores were absent (Plate II, Fig. 7; and Plate III, Fig. 13), while in other instances those which were seen were globular (Plate II, Fig. 6 and 9; and Plate III, Fig. 13). Also abnormally large globular melanophores, 5 to 6 times larger than the usual, were observed (Plate III, Fig. 12 and 13). These types of giant melanophores, however, were noted only rarely and could possibly be the result of fusion of several globular melanophores (Plate III, Fig. 13). The distribution of melanophores differed not only between animals but also in the same animal. In some cases the globular melanophores were observed between the normal ones (Plate II, Fig. 5 and 8; and Plate III, Fig. 11), while in others, regions with multibranched melanophores and globular melanophores could be distinguished. Areas with no melanophores were also noted (Plate II, Fig. 6, 7 and 9; and Plate III, Fig. 10 and 13).

MELANOPHORES IN THE IRRADIATED HEAD

Considerable difference was noted in comparing the melanophore damage in the irradiated head with that in the irradiated tail. Globular melanophores were found in some areas of the head, but they were comparatively rare and were usually isolated between normal melanophores—in the majority of cases 1–2 globular melanophores per microscopic field at the most (Plate IV, Fig. 14 and 15; and Plate V, Fig. 19). An area with 4–5 globular melanophores together was an exceptional finding in the head (Plate V, Fig. 18). Usually, most of the melanophores in the connective tissues, muscles and epithelium were completely normal (Plate IV, Fig. 14 and 15; and Plate V, Fig. 18 and 19). In many regions of the irradiated head, all melanophores in the connective tissues were normal and some globular melanophores were observed only in the epithelium (Plate IV, Fig. 16 and 17). Finally, in some regions of the irradiated head, all melanophores in all tissues were normal and the subepithelial pigment layer could not be distinguished from the pigment layer of control animals (Plate V, Fig. 20 and 21).

DISCUSSION

A comparison of the results of irradiation of the tails of young axolotls with those of the anterior portion of the heads under identical conditions shows clearly that radiosensitivity of melanophores in various portions of the body is quite different. This is in accordance with some of our previous observations. By irradiating the eye of the young axolotl,[10] it was discovered that "the pigment cells of choroid always react in a typical way to irradiation of the eye. Soon after irrdiation, an abnormal accumulation of the pigment cells was observed in the anterior portion of the retina and the iris near the lens. . . . The pigment cells are the most resistant cells in the eye and, therefore, they do not decrease in number even during complete degeneration of the eye after roentgen treatment. . . . This process of concentration of all pigment cells appeared



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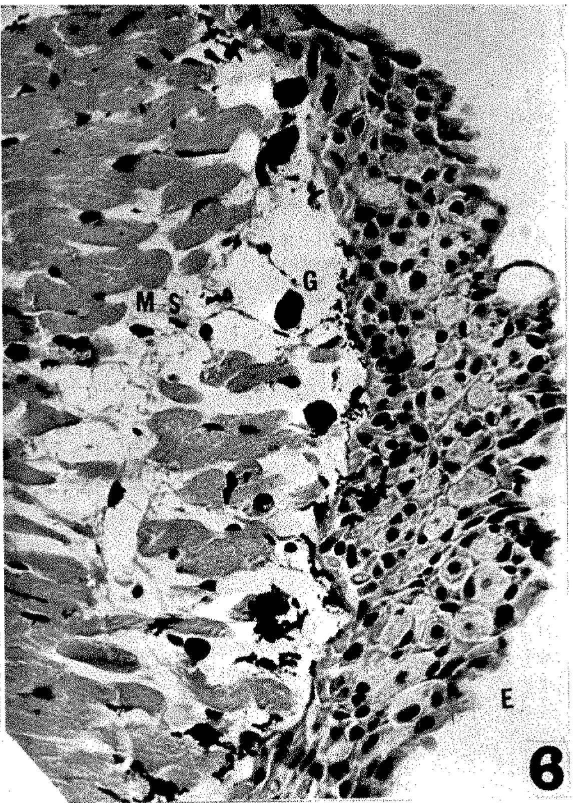

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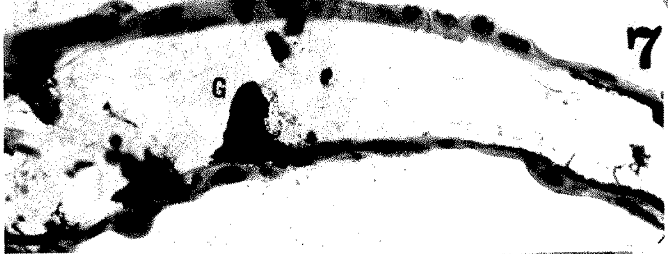

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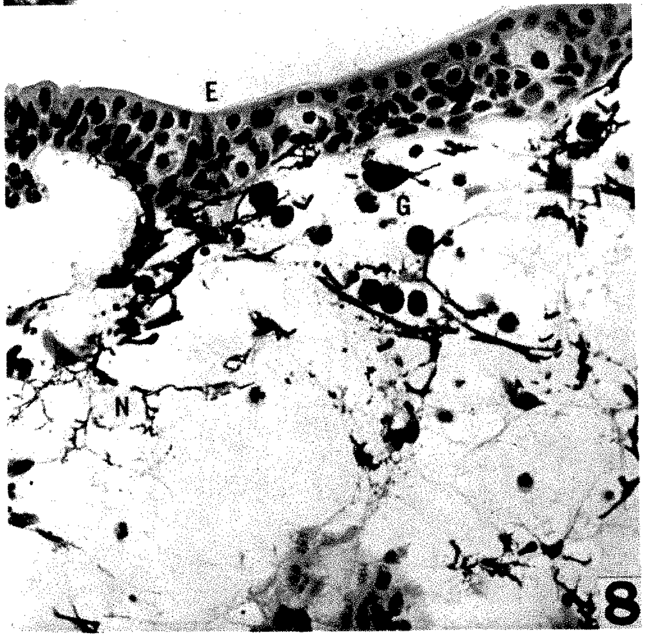

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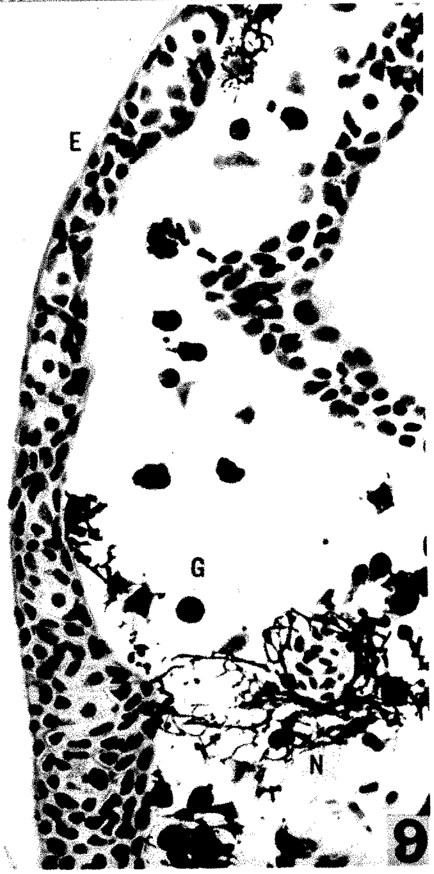

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exaggerated because of the simultaneous degeneration of all other components of the eye. Thus, after complete reduction, the rudiments of the eye consist only of a concentrated accumulation of pigment cells. . . . It is noteworthy that these pigmentary rudiments of the eye when observed long after the irradiation do not undergo further change."

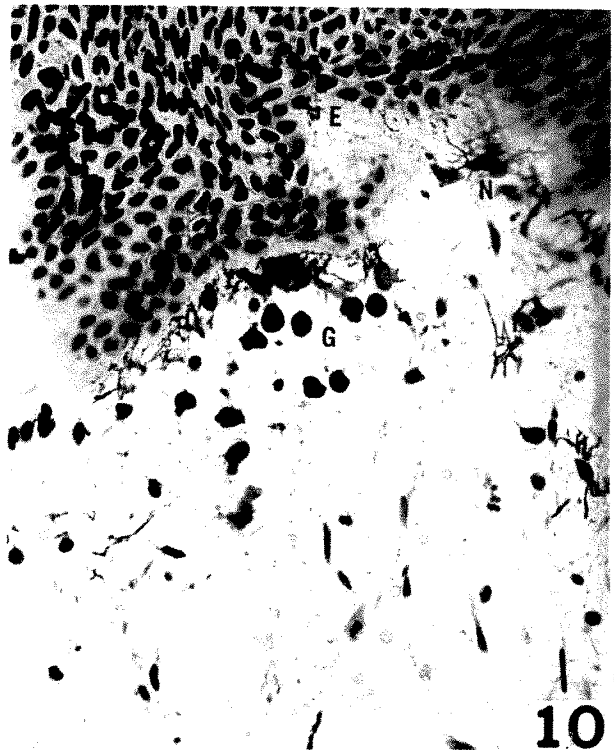
In some cases, roentgen irradiation can definitely stimulate the development of melanophores in some organs of the young axolotl.[11] Normal animals of this age have only a few pigment cells in the liver; however, an increase of melanophores was noted in their livers when only the heads were irradiated. Probably, changes in metabolism provoke this abnormal accumulation of melanophores. In some animals, these pigment cells accumulated in such number that the entire liver was black and only in some areas could the usual liver cells be found. Also, after total irradiation of adult axolotls[12] with 1,000 r, an increase in melanophores was observed in the liver. The number of these cells was greater than in control animals, but smaller than in young animals in which only the heads were irradiated. It has also been noted[19] that roentgen irradiation can provoke the development of melanophores in tissue, where they do not normally exist. Melanophores were never observed in the epithelium of the cornea in young axolotls; however, after irradiation with 500 to 9,000 r, the development of melanophores in irradiated epithelium of the cornea was typical. They had not developed after irradiation with 250 r. Melanophores appeared in irradiated epithelium as large, compact, globular cells or as branched pigment cells with many processes. In some cases, an accumulation of many small pigment granules was observed.

These observations have shown that the same cells (melanophores) can react differently to irradiation. There are varying degrees of sensitivity, depending mostly on their location. Those in the tail appear to be most sensitive and almost disappear after irradiation. Those located in the head are much more resistant, those in the eye are very resistant, and those in the liver are not only resistant but increase greatly in number after irradiation. Finally, melanophores were noted in large number in the epithelium of the cornea, which normally has no melanophores.

Until now, the process causing the disappearance of melanophores in the tail has not been clear. New observations, however, have shown that the activity of macro-

PLATE II

FIG. 5. Part of the section through the tail of animal fixed 70 days after irradiation with 1,500 r and 87 days after hatching. (E) Skin epithelium; (G) globular melanophores; (MS) muscles; (N) normal melanophores. Photomicrograph, ×100. FIG. 6. Part of the section through the tail of animal fixed 25 days after irradiation with 3,000 r and 49 days after hatching. (E) Skin epithelium; (G) globular melanophores; (MS) muscles. Photomicrograph, ×100. FIG. 7. Part of the section through the tail of animal fixed 35 days after irradiation with 1,500 r and 59 days after hatching. (E) Skin epithelium; (G) globular melanophores. Photomicrograph, ×100. Fig. 8. Part of the section through the tail of animal fixed 43 days after irradiation with 3,000 r and 67 days after hatching. (E) Skin epithelium; (G) globular melanophores; (N) normal melanophores. Photomicrograph, ×100. FIG. 9. Part of the section through the tail of animal 63 days after irradiation with 3,000 r and 97 days after hatching. (E) Skin epithelium; (G) globular melanophores; (N) normal melanophores. Photomicrograph, ×100.



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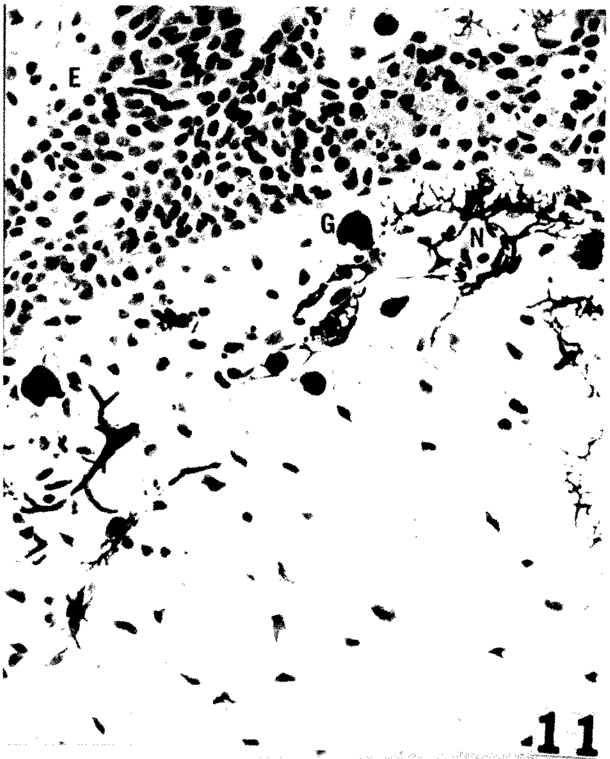

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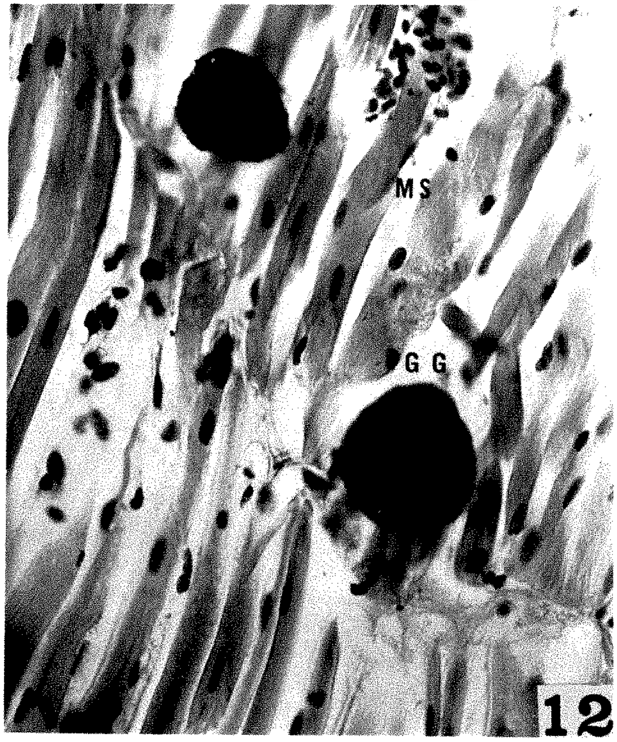

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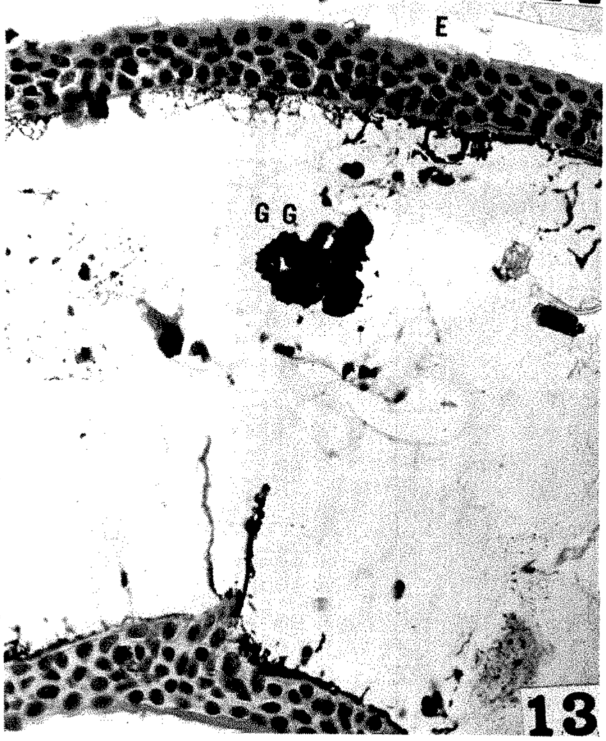

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Plate III

Fig. 10. Part of the section through the tail of animal 70 days after irradiation with 1,500 r and 94 days after hatching. (E) Skin epithelium; (G) globular melanophores; (N) normal melanophores. Photomicrograph, ×100. Fig. 11. Part of the section through the tail of animal 63 days after irradiation with 500 r and 87 days

phages could explain this phenomenon. In previous papers, the importance of the activity of macrophages in destroying various tissues was described.[13–17] It was shown that skeletal tissues, muscles, teeth and the lens gradually disappeared as a result of macrophage activity with phagocytosis and secretion of lytic enzymes dissolving the tissues. Now we have the first evidence of phagocytosis of pigment granules by macrophages. It was possible to see clearly on photomicrographs (Plate vi, Fig. 22, 23, 24, 25, 26 and 27) that some macrophages were in close contact with melanophores (Plate vi, Fig. 22, 25 and 27), and in the cytoplasm of macrophages many pigment granules were seen, obviously swallowed by these wandering cells. In some macrophages, there were so many pigment granules that the macrophages were almost as dark as the melanophores (Plate vi, Fig. 23, 24, 25 and 27). From these observations it is concluded that the macrophages destroyed irradiated melanophores in the region of the body where the number of melanophores was reduced after irradiation (the tail). Why they do not destroy melanophores in other regions is not known.

The various reactions of melanophores to irradiation in other amphibia have been described by several investigators. In tadpoles of *Rana clamitans*, redistribution of melanophores after irradiation was reported by Levine.[31] According to him, the melanophores contract and subsequently break up into a number of black droplets. Obviously, this phenomenon is similar to the formation of globular melanophores as described herein. Colwell and co-workers[23] described the response of melanophores to irradiation in the skin of tadpoles. After irradiation, complete withdrawal of processes, contraction and fragmentation of these cells were observed.

On the other hand, Luther[33] noted an increase in the amount of pigment in the skin of *Salamandra maculosa* after irradiation. Rugh[38] also observed an increase of pigmentation after irradiation with 25,000 r or 50,000 r in *Amblystoma opacum* larvae. Rugh stated that irradiation had two effects on chromatophores. "First, it tends to relax them and allows them to attain maximum size, thus darkening the larvae. Whether this effect is direct or is mediated through the nervous or hormonal system has not been determined. Within a very few hours after X-irradiation, the larvae can be easily identified when placed with controls, simply by the color difference. This accentuated pigmentation appears progressively to increase, not because of any increase in the number of chromatophores (which number is presumably fixed) but rather because of the relaxation of those present, and the further lightening of the controls." The melanophores after irradiation were "frozen" in the state of expansion. It, therefore, seems that in amphibia two opposite effects of radiation are present: contraction of melanophores, reducing the number of melanophores and decreasing pigmentation; and expansion of melanophores with an increase of pigmentation.

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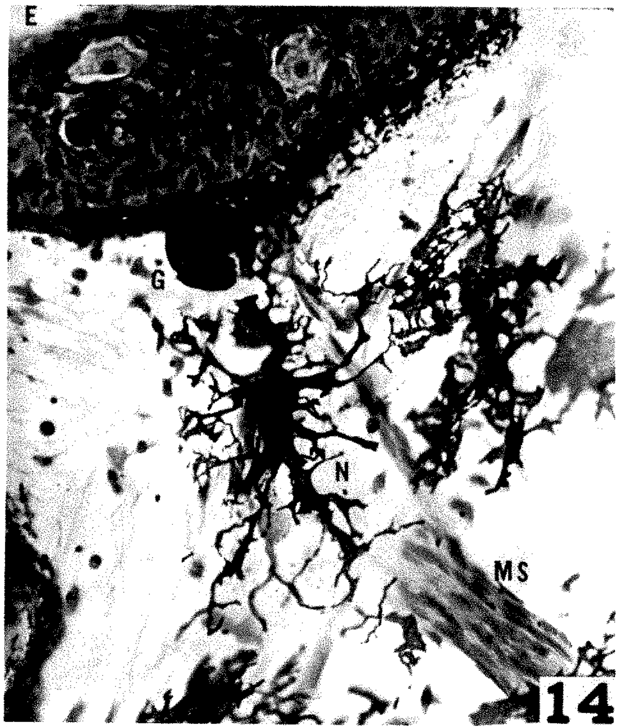
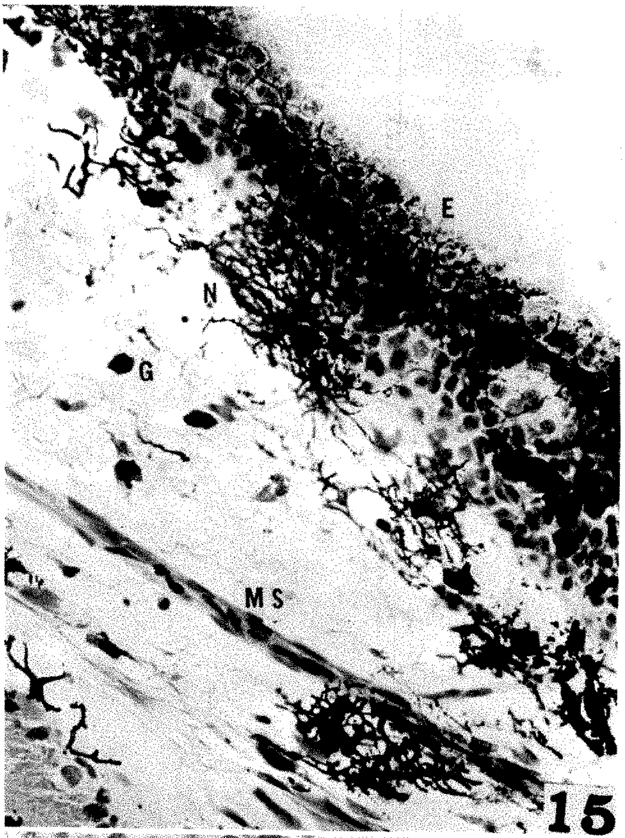
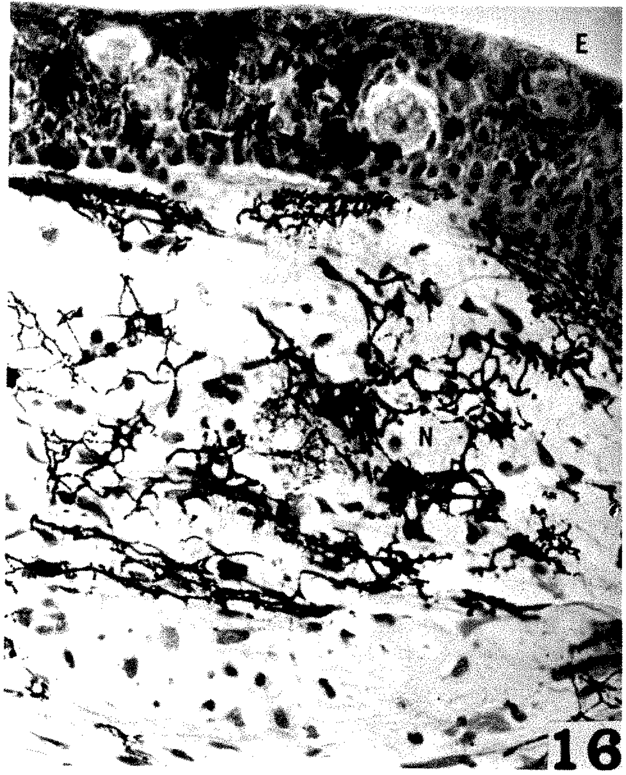
after hatching. (E) Skin epithelium; (G) globular melanophores; (N) normal melanophores. Photomicrograph, ×100. Fig. 12. Part of the section through the tail of animal 42 days after irradiation with 1,500 r and 66 days after hatching. (GG) Giant globular melanophore; (MS) muscles. Photomicrograph, ×100. Fig. 13. Part of the section through the tail of animal 49 days after irradiation with 500 r and 73 days after hatching. (E) Skin epithelium; (GG) giant globular melanophore. Photomicrograph, ×100.







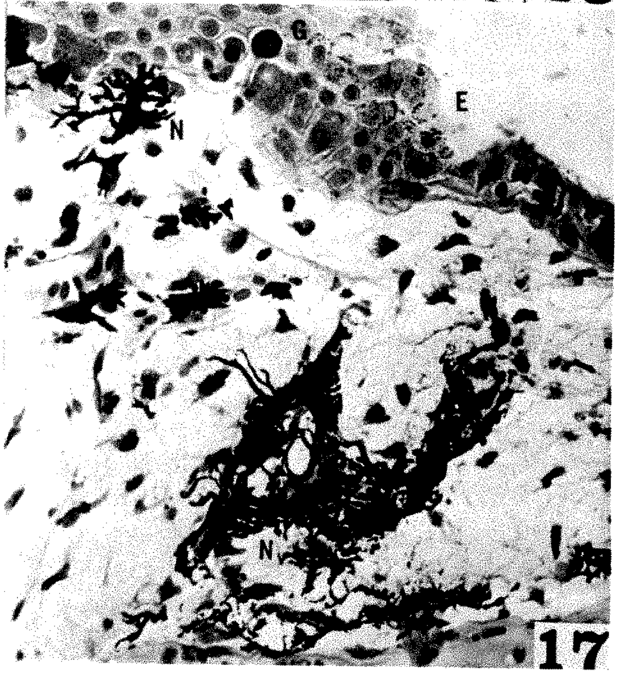


PLATE IV

FIG. 14. Part of the section through the head of animal 42 days after irradiation with 1,500 r and 66 days after hatching. (E) Skin epithelium; (G) globular melanophore; (MS) muscles; (N) normal melanophores. Photomicrograph, ×100. FIG. 15. Part of the section through the head of animal 70 days after irradiation

Various reactions of pigment cells to radiation are present not only in amphibia, but in other animals as well. In fish, for example, retardation of development of cutaneous melanophores was found in larvae of Chinook salmon after roentgen irradiation.[44] According to Welander and coworkers,[44] "the comparative slowness or lack of pigment development in irradiated as compared with control fish was noticeable about 24 days after exposures to 2,500, 5,000 and 10,000 r. Although the chromatophores were somewhat more expanded in irradiated fish, there were fewer chromatophores present than in the controls. This lack of pigment was one of the first pieces of evidence that development was being retarded in X-rayed fish." On the other hand, several investigators described an increase of pigmentation after irradiation. Smith[40] observed eruptions of melanophores 2 to 4 weeks after roentgen irradiation of goldfish (*Carassius auratus*). The production of melanophores may be so great as to cause a general cutaneous melanosis. Depigmentation occurs usually only after several weeks. According to Ellinger,[27] the minimum dose which produces pigmentation in goldfish is 800 r. In many instances, considerably higher doses failed to produce pigmentation. The pigmentation started on the head, spread to both sides of the trunk and was pronounced at the lateral lines, despite the fact that irradiation always took place in the dorsoventral position. Pigmentation was more marked when high doses were applied, with the fish's dorsal fin showing some black pigment prior to irradiation. Ellinger states that "roentgen pigmentation in albinotic goldfish is especially interesting because of the mechanism of this process: In mammals this phenomenon is explained on the assumption of a photochemical process. . . . Contrary to albinotic mammals, albinotic fish develop roentgen pigmentation. This directs attention to the fact that the chromatophores of fish are controlled by the nervous system. It is generally known that chromatophores of fish have a double innervation through sympathetic fibres (chromatodilatatores and chromatoconstrictores), and that there exists a chromatomotor nerve center in the medulla oblongata." This view is supported by the experiments of Davison and Ellinger.[25] These investigators showed that by irradiation of the brain in *Carassius auratus* the most pronounced damage was observed in the medulla oblongata, where the chromatomotor nerve center is located. Added support is found in the experiments of Von Frisch,[42] who produced in another fish (*Phoxinus laevis*) pigmentation throughout the entire body after mechanical destruction of the pigmento-motoric center in the medulla oblongata.

There are many reports in the literature concerning the effect of roentgen irradiation on pigment in mammals. A well known effect is the graying of the hair after treatment, a phenomenon described in detail by Hance.[29] He found that a few weeks after

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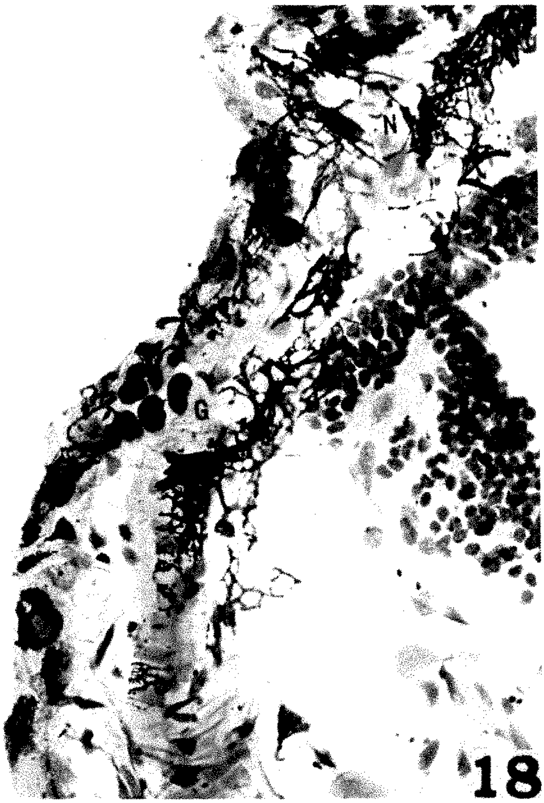
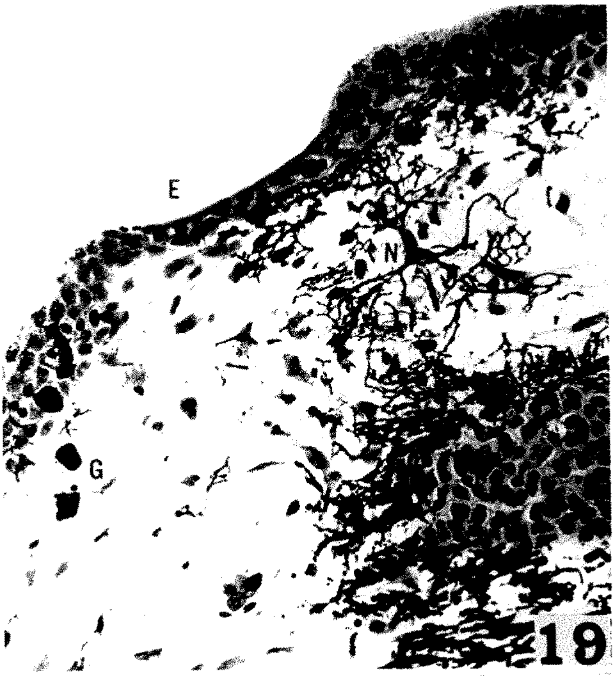
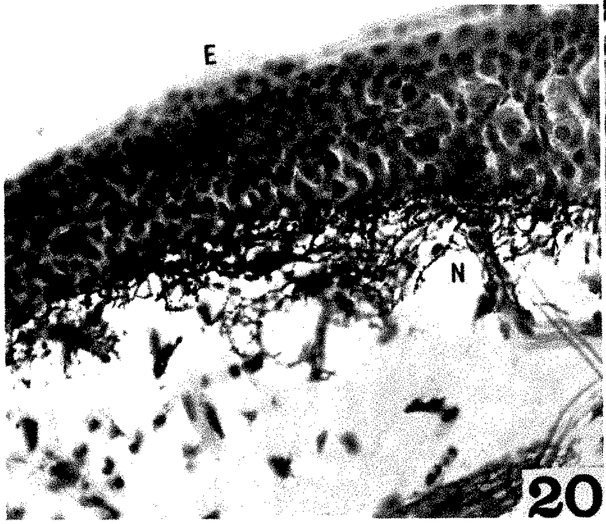
with 1,500 r and 94 days after hatching. (E) Skin epithelium; (G) globular melanophore: (MS) muscles; (N) normal melanophores. Photomicrograph, ×100. Fig. 16. Part of the section through the head of animal 43 days after irradiation with 3,000 r and 67 days after hatching. (E) Skin epithelium; (N) normal melanophores. Photomicrograph, ×100. Fig. 17. Part of the section through the head of animal 28 days after irradiation with 1,500 r and 52 days after hatching. (E) Skin epithelium; (G) globular melanophore; (N) normal melanophores. Photomicrograph, ×100.







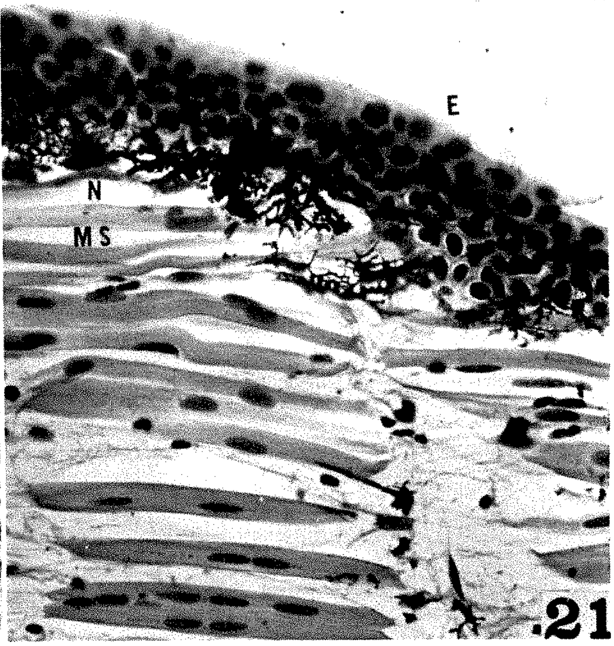


PLATE V

FIG. 18. Part of the section through the head of animal 37 days after irradiation with 3,000 r and 61 days after hatching. (G) Globular melanophores; (N) normal melanophores. Photomicrograph, ×100. FIG. 19. Part of the section through the head of animal 63 days after irradiation with 3,000 r and 87 days after hatching. (E) Skin epithelium; (G) globular melanophores; (N) normal melanophores. Photomicrograph, ×100. FIG. 20. Part of the section through the head of animal 32 days after irradiation with 500 r and 56 days after hatching. (E) Skin epithelium; (N) normal melanophores. Photomicrograph, ×100. FIG. 21. Part of the section through the head of animal 49 days after irradiation with 500 r and 73 days after hatching. (E) Skin epithelium; (MS) muscles; (N) normal melanophores. Photomicrograph, ×100.

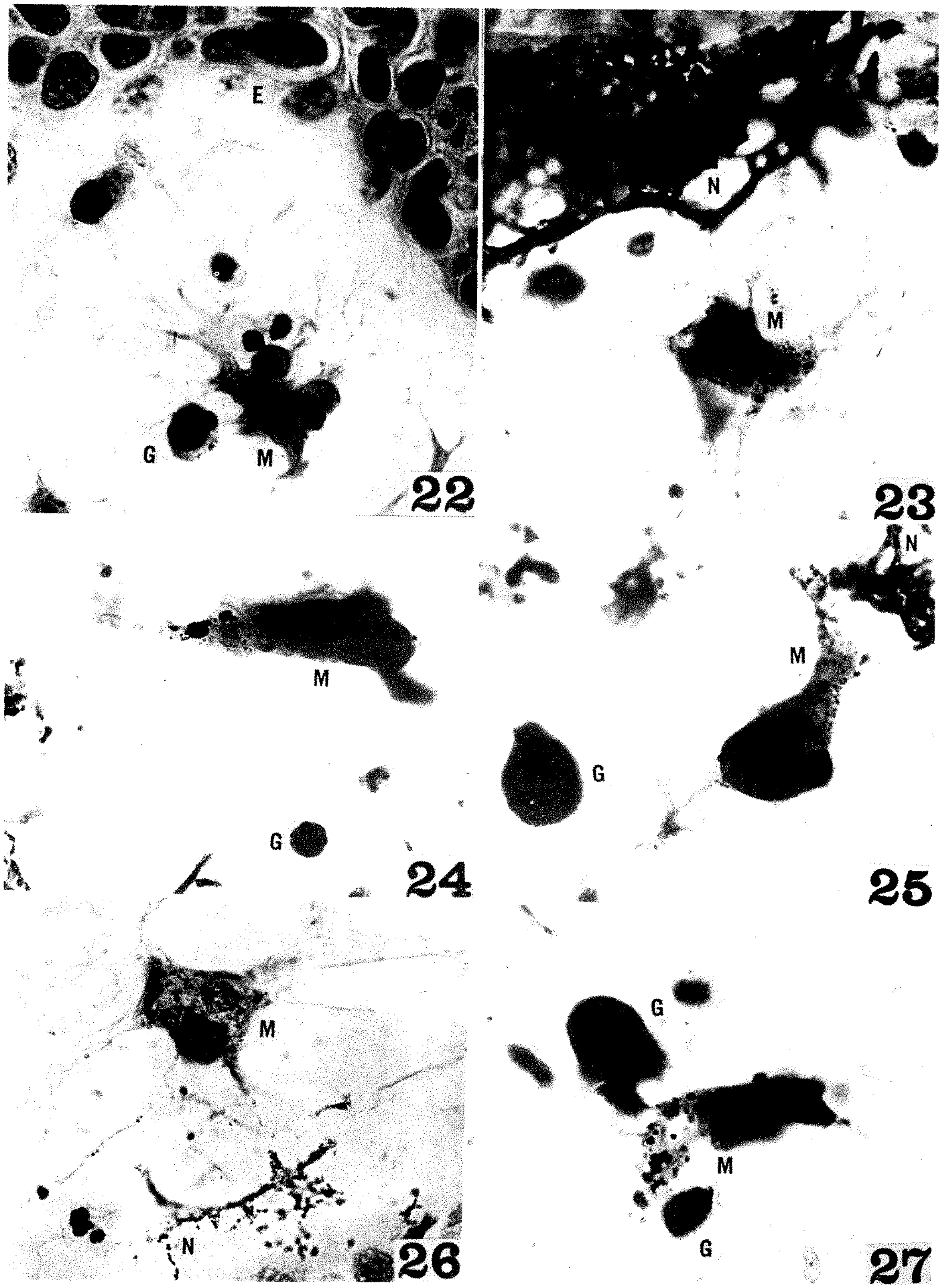


Plate VI

Fig. 22–27. Various portions of sections through the tail of animal 56 days after irradiation with 500 r and 80 days after hatching. The phagocytic activity of macrophages. (E) Skin epithelium; (G) globular melanophores; (M) macrophage; (N) normal melanophores. Photomicrograph, ×510.

roentgen irradiation the pigmented hair of mice fell out and was replaced with white hair. The condition persisted for 12 months without any indication of change. After local irradiation of small areas on the ventral side of mice, white hair appeared on the belly in about 1 month. Three months after exposure, it was noted that areas on the dorsal side of the animal that had been directly under the exposed belly, were beginning to whiten. The relatively small amounts of radiation turned the hair white without injuring the animals in any other way. Keeler[30] also described the graying of hair in the mouse and considered this reaction as an index of relative effectiveness of radiation. According to Lübnow,[32] a change of hairs occurred in rabbits after heavy roentgen irradiation. The cells of the matrix did not show any deep damage, but produced new unpigmented hairs. After irradiation with small doses, the development of partially pigmented hairs could be observed. The irradiated unpigmented skin of the rabbit is very similar morphologically and physiologically to the skin of the albino rabbit.

Dobrovolskaia-Zavadskaia and Rodzevitch[26] described a difference in the reaction to radiation of two strains of mice. Graying of the hair in one strain was more pronounced and more uniform than in the other. According to Chase and co-workers,[22] under standard conditions there exists a constant relationship between the dose administered and the degree of graying obtained. Loss of pigment does not occur in hair present at the time of irradiation, but only in hair developing afterward. Likewise, the degree of graying is more pronounced in hair which starts growing only after the treatment. Coloration remains approximately constant during the further life of the animal in spite of repeated hair generations.[9] Doses below 250 r cause no recognizable graying; doses of about 1,000 r result in complete decoloration. Graying of the hair in mice is produced by appropriate doses of roentgen rays, with both high and low energy rays (20 million volt and 200 kilovolt, respectively). Irradiation of the eye of the mouse during the first 8 days after birth has been noted to cause a quantitative reduction in pigment accumulation.[36] This reduction becomes apparent sometime between 8 and 16 days, depending on the time of irradiation. Evidently, one or more of the processes involved in pigment accumulation in the eye is relatively radiosensitive during the first few days after birth, but this radiosensitivity decreases progressively during the succeeding week or so. The production of white hair in black rats following freezing of the skin has also been reported.[41]

Decoloration of hair has not been observed in man.[22] Peck[34] described the development of a hyperpigmentation in the human skin after disappearance of the erythema as a result of thorium X irradiation. According to him, this hyperpigmentation may last for months and is due partly to prolonged pigment formation and partly to chromatophoric pigment in the cutis. A concentration of melanin in the skin of the mouse after irradiation with 5,000 r was described as follows:[1] "The entire follicle is laden with clumps of melanin. In the lower portion of the hair follicle, melanin is so abundant that it masks the histological details. . . .The epidermis also contains abundant extracellular melanin which forms either large clumps or small granules."

After daily gamma irradiation of mice, Quevedo and Grahn[37] found both graying of the body hair and hyperpigmentation of the extremities simultaneously. The darkening of the limbs is a function of both radiation intensity and total accumulated dose. Hyperpigmentation is the result of a direct effect of the irradiation of epidermal melanocytes, as shown by shielding experiments. These observations are important because they show the variability of reactions of pigment cells in mammals to irradiation, and are in complete accord with our observations on the axolotl. According to these authors, the melanocytes in the hair follicle apparently are more sensitive to irradiation than those situated in the basal layer of the epidermis. Hyperpigmentation was also observed in human subjects after exposure to ionizing radiations. Erythema doses have been reported to cause hyperpigmentation in the presence of slight skin damage.[28] A study of the Marshallese natives who were exposed to radioactive fall-out has shown that hyperpigmentation was connected with severe injury where the dosage to the surface tissues may have exceeded 1,000 to 1,500 r. Some degree of darkening was evident for many months after exposure, even when other evidence of tissue injury had decreased.[24]

The general conclusion drawn from this survey of the literature is that the behavior of pigment cells after irradiation, in all groups of animals and human subjects, differs in various cases. In each group of animals, many examples of the destructive effect of roentgen irradiation, which results in the decrease or even the disappearance of pigmentation, can be found. On the other hand, the opposite effect of irradiation in the same group of animals, *i.e.*, increase of pigmentation has also been reported. Although the varying radiosensitivity of pigment cells is a well established fact, the reason for this has not been determined.

SUMMARY

1. The anterior portion of the heads in 3 groups of 77 young axolotls (24 days after hatching) was irradiated with 500, 1,500 and 3,000 r, respectively; in 3 other groups (78 animals of the same age), the tails were irradiated on the same day with the same doses; 1 group of 20 animals from the same spawning served as untreated controls.

2. In the irradiated tails, the number of melanophores was reduced. Most of the melanophores were abnormal. They had either a globular or an irregular form without any processes. The long multibranched outgrowths of melanophores could be seen in only a few areas. In some regions of irradiated tails, the melanophores were either absent or uniformly globular. In rare instances globular melanophores of giant size could be observed.

3. Globular melanophores were also noted in the irradiated head, but they were comparatively rare and usually isolated between normal melanophores. In some regions of the irradiated head, all the melanophores in all tissues were normal.

4. The reduction in the number of the melanophores in the tail can be explained by the activity of macrophages, which phagocytize irradiated melanophores.

5. This investigation showed that a considerable difference in melanophore radiosensitivity exists in tail and head regions. This is in accordance with previous observations. The resistance to radiation of the pigment cells of the choroid of the eye and the stimulation by irradiation of the development of pigment cells in the liver and cornea of the axolotl are discussed.

6. A survey of the literature shows that in amphibia, fish, mammals and man, roentgen irradiation in some cases has a destructive influence on pigment cells and, after treatment, a decrease or even disappearance of pigmentation is observed. In other cases in the same groups of animals, an increase of pigmentation is noted. Varying radiosensitivity and varying reactions of pigment cells to irradiation are thus established facts.

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EDITORIALS

THE FORTY-SEVENTH ANNUAL MEETING OF THE AMERICAN RADIUM SOCIETY

THE Forty-seventh Annual Meeting of the American Radium Society will be held on April 8, 9 and 10, 1965, at the Roosevelt Hotel in New Orleans, Louisiana. This will be the third visit of the Society to New Orleans; the first was a one day meeting held in the Scottish Rite Cathedral on April 26, 1920, and followed by a banquet in the Hotel De Soto. Twenty members answered the roll call. Highlights of the scientific program included a symposium on the "Use of Radium in Malignancy" and a paper by Dr. Henry H. Janeway on the "Use of Emanation in the Treatment of Malignant Tumors." Dr. Janeway was not present because of illness and his presentation was read by Dr. G. Failla. Dr. J. M. Martin of Dallas, Texas, was complimented by those present on a novel presentation by a "moving picture" demonstrating early and late cases of cancer treated by radiotherapy. The Research Committee proposed a schedule or form for recording stages of disease and treatment data and also urged a careful record of follow-up examinations. It was at this meeting, moreover, that in response to an invitation from its Editor, Dr. H. M. Imboden, the AMERICAN JOURNAL OF ROENTGENOLOGY was adopted as the official publication of the Society.

During the intervening years there have been tremendous advances in medical science and in all clinical branches of medicine. This progress has led to increasing specialization that has advantages but also incurs the danger of placing biased emphasis on single methods of treatment. The diagnosis or treatment of cancer, regardless of its anatomic site of origin, is not a narrow specialty. It seems timely to re-emphasize the need for more attention to unprejudiced approaches and the use of combined therapy for cure as well as palliation. With this thought in mind and in response to requests by the membership, the Scientific Program Committee has endeavored to arrange a program of breadth as well as depth. The subjects have been selected not only to cover current therapeutic and diagnostic measures but work in progress or in the early stages of investigation.

The Janeway Lecture, always a leading feature, will be given by Dr. T. A. Watson, Director of the Ontario Cancer Foundation, London Clinic, Victoria Hospital, London, Canada. The title of his lecture is "Cancer of the Breast." Our distinguished guest will be Professor D. W. Smithers, Director of the Radiotherapy Department of the Royal Marsden Hospital, London, England. Professor Smithers will speak on "Some Aspects of Radiotherapy in Relation to Thyroid Carcinoma" and will also participate in a panel discussion organized by Philip Rubin, M.D., on the "Management of Solitary Metastases." Three symposia will be presented. These have been arranged by the respective chairmen and are as follows: "A Critical Analysis of Some Diagnostic Tests Using Radioactive Isotopes," Edith H. Quimby, Ph.D., Chairman; "Variation of Cellular Radiosensitivity with the Mitotic Cycle," Juan A. del Regato, M.D., Chairman; and "The Management of Regional Lymph Nodes in Breast Cancer," Robert C. Hickey, M.D., Chairman.

Participants from other countries will include Vera M. Dalley, M.D., London, England, E. Millington, M.D., Brighton, England, and Rafael Martinez, M.D., Mexico City, Mexico. A complete list of speakers and their subjects is given in the Preliminary Program which appears elsewhere in this issue of the JOURNAL.

There is much for the visitor to do and see in New Orleans. It is a modern city that has preserved the charm of its historic past and is widely known for its hospitality and excellent dining facilities. The Arrangements Committee with Manuel Garcia, M.D., Chairman, ably assisted by R. Lee Foster, M.D., Richard H. Jesse, M.D., Seymour F. Ochsner, M.D. and John Day Peake, M.D., is preparing special attractions for the ladies. On Thursday morning plans have been made for a late breakfast at one of the well-known restaurants followed by a walking tour of the French Quarter. On Friday there will be a Garden District and a Plantation bus tour with lunch. On Thursday evening the Society will again be indebted to the Radium Chemical Company for providing what will be a relaxing and memorable social occasion. The Annual Banquet, which features the presentation of the Janeway Medal as well as entertainment and dancing, will be held Friday evening.

A cordial welcome is extended to all who are interested in the activities of the American Radium Society. Members of the Society will receive advance registration forms. Please return them promptly. Nonmembers will be charged a nominal registration fee and are urged to register and make reservations through the Chairman of the Arrangements Committee, Dr. Manuel Garcia, Charity Hospital of Louisiana, New Orleans, Louisiana. Accommodations will be assigned in the order in which requests are received.

Every effort is being made by the officers and committee members to make the Forty-seventh Annual Meeting of the American Radium Society a scientific success and a social pleasure. We hope you will attend.

JOSEPH H. FARROW, M.D.
President, American Radium Society

112 East 74th St.
New York, New York 10021

L. R. SANTE, M.D.
1890-1964

L. R. SANTE, one of the most distinguished pioneer radiologists, died at the age of 74 years at St. Mary's Hospital, St. Louis, Missouri, on October 27, 1964, following a cerebral accident.

Dr. Sante was born in St. Louis, Missouri, in 1890. He received his premedical education at Washington University School of Medicine, St. Louis, Missouri, from which he received his medical degree in 1913.

After one year of internship at the St. Louis City Hospital and a year of general practice in St. Louis, he moved to Ellendale, North Dakota, where he continued the general practice of medicine until he entered Military Service in 1917. After indoctrination at Camp Greenleaf, Fort Ogelthorpe, Georgia, he transferred to the Army School of Roentgenology because of his interest in previous work with x-ray. After completion of his training, he was assigned to the x-ray department at Debarkation Hospital, No. 5, New York City, in association with Dr. William H. Stewart.

In 1919, he was appointed Director of Radiology at the St. Louis City Hospital and continued in this capacity until 1946, following which he became a consultant. Also in 1919 he accepted a position as Instructor in Radiology at St. Louis University and within a short period became Professor and Director of the Department of Radiology at the St. Louis University School of Medicine and the St. Mary's Hospital Group. He continued in this capacity until his retirement in 1960.

Dr. Sante was a prolific writer and published more than 125 scientific articles and seven books on radiology. Approximately 75 radiologists received their training under his direction in the residency programs. As a teacher and counselor of young men, he was at his best and no problem was too great or too trivial for his close attention.

Dr. Sante was a member of the American Roentgen Ray Society, the American Radium Society, the Radiological Society of North America and a Fellow of the American College of Radiology. He received the American College of Radiology Gold Medal in 1959. He was a charter member of the American Board of Radiology and for many years one of its examiners. He was also a Fellow in the American College of Physicians and a member of the Alpha Omega Alpha and Sigma Xi. He was past President of the St. Louis Medical Society and the St. Louis Society of Radiologists. He was also past First-Vice President of the American Roentgen Ray Society and the American Radium Society. He held honorary membership in the British, Mexico and Panama Society of Radiologists.

Dr. Sante is survived by his wife, Jewel, a daughter, Mrs. Carl Weaver of Cleveland, Ohio, and a son, Henry Evatt of St. Louis, seven grandchildren and one great grandchild.

Don C. Weir, M.D.

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AMERICAN RADIUM SOCIETY

PRELIMINARY PROGRAM

The following is the tentative program arranged by the Scientific Program Committee for the Forty-seventh Annual Meeting of the American Radium Society to be held at the Roosevelt Hotel, New Orleans, Louisiana, April 8–10, 1965.

Wednesday, April 7, 1965

10:30 A.M.—5:00 P.M.
Executive Committee Meeting (Baronne Room).

1:00 P.M.—5:00 P.M.
Registration (Mirror Room).

Thursday, April 8, 1965

8:00 A.M.—5:00 P.M.
Registration (Mirror Room).

8:15 A.M.
First Executive Session—for All Members.

9:00 A.M.
Opening Ceremonies and Welcome Address.
Louis J. Bristow, Jr., M.D., President of the Radiological Society of Louisiana, New Orleans, Louisiana.
Joseph H. Farrow, M.D., President, American Radium Society, Memorial Hospital for Cancer and Allied Diseases, New York, New York.

First Scientific Session
Robert C. Hickey, M.D., Chairman.
University Hospital, Madison, Wisconsin.

9:15 A.M.
Lymphangiography As an Adjuvant to Pelvic Radium Dosimetry. Carl Fabian, M.D.,* Stanford University School of Medicine, Palo Alto, California, and David Benninghoff, M.D.,* Kings County Hospital Center, Brooklyn, New York.

9:30 A.M.
Results of Cobalt 60 Rotation Therapy in Carcinoma of the Cervix. George P. Koeck, M.D., Lillian E. Jacobson, M.A., and William B. Hillsinger, B.S.,* United Hospitals of Newark, Newark, New Jersey.

9:45 A.M.
Carcinoma of the Cervix Uteri Associated with Pregnancy. Antonio Bosch, M.D.,* and Victor A. Marcial, M.D., Puerto Rico Nuclear Center, Rio Piedros, Puerto Rico.

10:00 A.M.
Pelvic Exenteration for Extensive Visceral Necrosis Following Radiation Therapy for Gynecological Cancer. Hugh R. K. Barber, M.D.,* and Alexander Brunschwig, M.D., Memorial Hospital for Cancer and Allied Diseases, New York, New York.

10:15 A.M.
Discussion of Previous Papers.

10:30 A.M.
Coffee Break.

10:45 A.M.
Combined Irradiation and Regional Chemotherapy in the Treatment of Retinoblastoma. Edward T. Krementz, M.D.,* Joseph V. Schlosser, M.D.,* and Joseph P. Rumago, M.D.,* Charity Hospital, New Orleans, Louisiana.

11:00 A.M.
Combined Irradiation and Methotrexate Treatment of Squamous Cell Carcinoma of the Head and Neck. Milton Friedman, M.D., and John F. Daly, M.D.,* University Hospital, New York, New York.

11:15 A.M.
The Value of Chemotherapy in the Irradiation of Ovarian Carcinoma. Emanuel E. Schwartz, M.D., and David M. Sklaroff, M.D.,* Albert Einstein Medical Center, Northern Division, Philadelphia, Pennsylvania.

11:30 A.M.
Radiotherapy and Surgery in the Treatment of Carcinoma of the Bladder: University of Maryland Experience. Fernando G. Bloedorn, M.D., Morris J. Wizenberg, M.D.,* and John D. Young, Jr., M.D.,* University of Maryland Hospital, Baltimore, Maryland.

11:45 A.M.
The Combined Treatment of Carcinoma of the Rectum with Cobalt and Chemotherapy. E. Millington, M.D.,* Royal Sussex County Hospital, Brighton, England.

12:00 NOON
Palliation of Metastatic Tumors of the Soft Somatic Tissues with Combined Radiation and Triple Chemotherapy. David W. Molander, M.D., Memorial Hospital for Cancer and Allied Diseases, New York, New York.

12:15 P.M.
Combined Therapy in Malignant Lymphoma. Eugene L. Bronstein, M.D., and William Geller, M.D.,* Memorial Hospital for Cancer and Allied Diseases, New York, New York.

12:30 P.M.
Discussion of Previous Papers.

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* By invitation

* By invitation

12:45 P.M.
Adjournment of First Scientific Session.

SECOND SCIENTIFIC SESSION
Marvin M. D. Williams, Ph.D., Chairman.
Mayo Clinic, Rochester, Minnesota.

2:00 P.M.
Modification of Radiation Response of Tissues by Actinomycin—Clinical Evaluation. Klaus Ranniger, M.D.,* and Melvin L. Griem, M.D., University of Chicago, Chicago, Illinois.

2:15 P.M.
The Radio-Protective and Anti-Tumor Effect of a New Antibiotic (Roche 5-9000). Donald R. Cole, M.D.,* Brenda B. Dreyer, B.S.,* Louis M. Rousselot, M.D.,* and Moses D. Tendler, Ph.D.,* St. Vincent's Hospital, New York, New York.

2:30 P.M.
Oxygen Effect Factor and Tumor Volume in C_3H Mammary Mouse Carcinoma System. Herman D. Suit, M.D.,* and Morimasa Maeda, M.D.,* M. D. Anderson Hospital and Tumor Institute, Houston, Texas.

2:45 P.M.
Hybaroxic Radiotherapy: Some Observations in the Development of Clinical Application and Technique. Orliss Wildermuth, M.D., Tumor Institute of the Swedish Hospital, Seattle, Washington.

3:00 P.M.
Evaluation of Lymph Node Function Following Irradiation or Surgery. Prentiss M. Dettman, M.D.,* E. Richard King, M.D., and Yale H. Zimberg, M.D.,* Medical College of Virginia, Richmond, Virginia.

3:15 P.M.
The Role of Regional Radiotherapy in Organ Transplantation. J. V. Schlosser, M.D.,* Charity Hospital of Louisiana, New Orleans, Louisiana.

3:30 P.M.
Comparative Study of Effects of Laser and/or Ionizing Radiation Therapy on Experimental Malignant Tumors. Paul E. McGuff, M.D.,* Tufts-New England Medical Center, Boston, Massachusetts.

3:45 P.M.
Discussion of Previous Papers.

4:00 P.M.
Symposium:
Variation of Cellular Radiosensitivity with the Mitotic Cycle. Juan A. del Regato, M.D., *Chairman*, Penrose Cancer Hospital, Colorado Springs, Colorado.
Variation in the Radiosensitivity of HeLa Cells during the Mitotic Cycle. L. J. Tolmach, Ph.D.,* Mallinckrodt Institute of Radiology, Washington University School of Medicine, Saint Louis, Missouri.
Cyclic Variations in Radiation Response in L Cells. Gordon Whitmore, Ph.D.,* University of Toronto, Toronto, Canada.
H Responses to Radiations in Hamster Cells. Warren K. Sinclair, Ph.D.,* Argonne National Laboratory, Argonne, Illinois.

5:15 P.M.
Adjournment of Second Scientific Session.

6:30 P.M.—8:30 P.M.
Reception—Grand Ballroom, Royal Orleans Hotel. Courtesy of the Radium Chemical Company.

Friday, April 9, 1965

7:45 A.M.
Second Executive Session (Breakfast Meeting for All Members).

8:30 A.M.—5:00 P.M.
Registration (Mirror Room).

THIRD SCIENTIFIC SESSION
John H. Maus, M.D., Chairman.
Ontario Cancer Foundation, Windsor Clinic, Metropolitan General Hospital, Windsor, Ontario, Canada.

9:00 A.M.
Symposium:
The Management of Regional Lymph Nodes in Breast Cancer. Robert C. Hickey, M.D., *Chairman*, University Hospital, Madison, Wisconsin.
A Rationale for a Simplified Surgical Treatment in Breast Cancer. George C. Crile, Jr., M.D.,* Cleveland Clinic, Cleveland, Ohio.
Pre- or Post-Operative Radiation Therapy for Breast Cancer? E. C. White, M.D.,* M. D. Anderson Hospital and Tumor Institute, Houston, Texas.
Rationale of an Extended Operation for Mammary Cancer. Jerome A. Urban, M.D., Memorial Hospital for Cancer and Allied Diseases, New York, New York.
Role of Supervoltage Irradiation for Regional Lymph Node Bearing Areas in Breast Cancer. Ruth J. Guttmann, M.D., Francis Delafield Hospital, New York, New York.

10:15 A.M.
Coffee Break.

10:30 A.M.
Evaluation of Radiotherapeutic Management of Intracranial Glial Tumors without Prior Surgery. Ivor Fix, M.D.,* Mount Sinai Hospital, New York, New York.

10:45 A.M.
The Place of Radiotherapy in Treatment of Ma-

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* By invitation

* By invitation

lignant Metastatic Glands of the Neck. Vera M. Dalley, M.D.,* Royal Marsden Hospital, London, England.

11:00 A.M.
Radiation Therapy of Carcinoma of the Vocal Cords without Mucosal Reaction—Five Year Results. Franz J. Buschke, M.D., and Jerome M. Vaeth, M.D., University of California Hospitals, San Francisco, California.

11:15 A.M.
Analysis of Complications following Megavoltage Therapy for Squamous Cell Carcinoma of the Tonsillar Area. Burton P. Grant, M.D.,* Vanderbilt University Hospital, Nashville, Tennessee, and Gilbert H. Fletcher, M.D., M. D. Anderson Hospital and Tumor Institute, Houston, Texas.

11:30 A.M.
Multiple Primary Cancers of the Upper Respiratory and Alimentary Tracts. A. J. Ballantyne, M.D., and R. D. Lindberg, M.D.,* M. D. Anderson Hospital and Tumor Institute, Houston, Texas.

11:45 A.M.
Discussion of Previous Papers.

12:00 NOON
Some Aspects of Radiotherapy in Relation to Thyroid Cancer. Professor D. W. Smithers,* Director of Radiotherapy Department, Royal Marsden Hospital, London, England.

12:30 P.M.
Adjournment of Third Scientific Session.

FOURTH SCIENTIFIC SESSION
Sidney Rubenfeld, M.D., Chairman.
Bellevue Hospital, New York, New York.

2:00 P.M.
Panel Discussion: The Management of Solitary Metastases. Philip Rubin, M.D., *Moderator*, Strong Memorial Hospital, Rochester, New York.

Panelists: Professor D. W. Smithers,* Royal Marsden Hospital, London, England; Danley P. Slaughter, M.D.,* Presbyterian Hospital, Chicago, Illinois; Oscar Creech, Jr., M.D.,* Charity Hospital of Louisiana, New Orleans, Louisiana.

3:15 P.M.
Observations on the Accidental Exposure of a Family to a Cobalt 60 Source. Rafael Martinez, M.D.,* Guillermo Cassab, M.D.,* Gustavo Ganem, M.D.,* Elias Guttman, M.D.,* Mario Lieberman, M.D.,* Lutz Vater, M.D.,* Max Linares, M.D.,* and Hector Rodriguez, M.D.,* Mexico City, Mexico.

3:30 P.M.
An Evaluation of Treatment Methods for Lung Carcinoma. Justin J. Stein, M.D., University of California at Los Angeles, Center for Health Sciences, Los Angeles, California.

3:45 P.M.
Discussion of Previous Papers and Recess.

4:00 P.M.
THE JANEWAY LECTURE

Cancer of the Breast. T. A. Watson, M.D., Ontario Cancer Foundation, Victoria Hospital, London, Ontario, Canada.

5:00 P.M.
Adjournment of Fourth Scientific Session.

7:00 P.M.
Reception and Annual Banquet—Roosevelt Hotel.

Saturday, April 10, 1965

8:30 A.M.
Third Executive Session.

FIFTH SCIENTIFIC SESSION
Roald N. Grant, M.D., Chairman.
American Cancer Society, Inc., New York, New York.

9:00 A.M.
Symposium:
A Critical Analysis of Some Diagnostic Tests Using Radioactive Isotopes. Edith H. Quimby, Ph.D., *Chairman*, College of Physicians and Surgeons, New York, New York.

Bone Scanning with Radioactive Strontium. N. O. Charkes, M.D.,* Albert Einstein Medical Center, Northern Division, Philadelphia, Pennsylvania.

Visualization of the Pancreas by Means of Photoscanning. E. Richard King, M.D., Medical College of Virginia, Richmond, Virginia.

Regional Pulmonary Blood Flow by Radioisotope Scanning. Henry N. Wagner, Jr., M.D.,* David C. Sabiston, Jr., M.D.,* John G. McFee, M.D.,* Donald Tow, M.D.,* and Howard S. Stern, M.D.,* Johns Hopkins Medical Institutions, Baltimore, Maryland.

Placental Localization with Radioactive Isotopes. Philip M. Johnson, M.D.,* and John J. Sciarra, M.D.,* The Presbyterian Hospital, New York, New York.

10:30 A.M.
Coffee Break.

10:45 A.M.
Cyclotron-produced Short-lived Radioactive Isotopes. Michel M. Ter-Pogossian, Ph.D., Washington University School of Medicine, Saint Louis, Missouri.

11:00 A.M.
The Place of Lymphangioadenography in the Diagnosis and Treatment of Malignant Disease. Mario Vuksanovic, M.D.,* and Manuel Via-

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* By invitation

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monte, Jr., M.D.,* Jackson Memorial Hospital, Miami, Florida.

11:15 A.M.

Hormonal Urinary Excretion in Carcinoma of the Cervix. Albert Segaloff, M.D.,* Ochsner Foundation Hospital, and Manuel Garcia, M.D., Charity Hospital of Louisiana, New Orleans, Louisiana.

11:30 A.M.

How to Irradiate Cervix Cancer without Accidentally Irradiating Yourself. Ulrich K. Henschke, M.D., and Basil S. Hilaris, M.D.,* Memorial Hospital for Cancer and Allied Diseases, New York, New York.

11:45 A.M.

Evaluation of Methods of Computer Estimation of Interstitial and Intracavitary Dosimetry. William E. Powers, M.D., and L. J. Tolmach, Ph.D.,* Washington University School of Medicine, St. Louis, Missouri.

12:00 NOON

Cylindroma. John C. Evans, M.D., Albert Einstein College of Medicine, Bronx, New York.

12:15 P.M.

The Etiology and Pathology of Buccal Mucosa Cancer in South India. Carl F. von Essen, M.D., Yale University School of Medicine, New Haven, Connecticut, A. D. Singh, M.D.,* and C. S. Small, M.D.,* Christian Medical College Hospital, Vellore, South India.

12:30 P.M.

Discussion of Previous Papers.

12:45 P.M.

Final Executive Session and Installation of New Officers. Adjournment of Forty-seventh Annual Meeting of the American Radium Society.

* By invitation

* By invitation

COLEGIO INTERAMERICANO DE RADIOLOGÍA

RECOMMENDATIONS ON THE TEACHING OF RADIOLOGY IN AMERICA

AT THE recent meeting of the Inter-American College of Radiology, held during the Eighth Inter-American Congress of Radiology at Caracas, Venezuela, October 2–9, 1964, a thorough study was made of the ways in which the teaching of radiology is carried out in all of the countries of America. A Symposium on "Teaching of Radiology in America" was conducted in which Drs. Eugene P. Pendergrass of the United States, Baudelio Villaneuva of Mexico, Amadeo Riera of El Salvador, Roberto Calderon of Nicaragua, Pedro Gonzalez Rincones of Venezuela, Oscar Soto of Peru, Walter Bomfim Pontes of Brazil, Francisco Cifarelli of Argentina, and Leandro Zubiaurre of Uruguay participated. This was followed by a number of very authoritative discussions.

The following resolution was adopted:

"The Inter-American College of Radiology, in view of the extraordinarily large advances attained in the field of Radiology, the growing importance of its application in medicine which is often decisive in the diagnosis or treatment of many diseases, as well as the enormous possibilities it offers for research:

"And, whereas, the present status of the Teaching of Medical Radiology in many of the nations of America is seriously deficient as it is not being carried out in a way which the study of this subject merits in accordance with the ever-increasing demand for more radiologists prevalent in the majority of the countries of our Continent:

"Addresses the respective university centers responsible for medical training in order to inform them about the following recommendations approved by the College."

These recommendations are:

1. Every Medical School should have a Department of Radiology which includes the disciplines of Radiodiagnosis, Radiobiology, Radiotherapy and Nuclear Medicine. This Department will be responsible for the organization, direction and the respective training at the undergraduate level of medical students, and postgraduate training for the preparation of Radiologists and further training of the same.

2. The Department of Radiology should have the latest and most complete equipment as well as the physical plant required by present day Radiology. All that pertains to radiology in the hospital where the Department is located shall be centralized therein.

UNDERGRADUATE TRAINING

3. Medical Radiology should be considered as an independent Division within the curriculum of the Medical School and should have the same prerogatives, privileges and obligatory examinations as the others do. All of the professors should be competent Radiologists and should dedicate their time exclusively to this special field.

4. During the Preclinical cycle (Basic Sciences), the teaching of radiology shall consist of the cooperation and assistance which the Division of Radiology shall extend to the teaching plan drawn up by the professors of the basic subjects and particularly to that of Radiation Physics.

5. During the Clinical cycle, the basic elements of Radiobiology, Radiotherapy and Nuclear Medicine will be included with Radiodiagnosis.

This training for medical students shall be distributed over several years of study in progressive order of complexity, attempting to obtain adequate coordination with the basic and clinical subjects in accordance with the general program established by the Division.

POSTGRADUATE TRAINING

6. Training for specialists should be planned and directed exclusively by the Universities through their Graduate Schools, under the control of their Departments of Radiology.

7. The duration of the course of specialization shall be not less than 3 years. There shall be a course in Radiodiagnosis and another in Radiotherapy, each with its own program of study and specialized teaching personnel. The first periods of both may be joint, covering radiation physics, radiobiology, pathologic anatomy, rudiments of mathematics, genetics and statistics.

8. During the final year, an examination shall be given, and this shall be a requirement for the Diploma of specialist; later on, a special project shall be undertaken which shall be graded by the teaching staff of the Department of Radiology.

9. The internationally recognized Societies of Radiology shall petition the governments that the academic degree or diploma be required in order to practice the profession of Radiology.

10. The Universities shall encourage the further training and scientific review of their teaching staffs in radiology, facilitating this by making it possible to attend a larger number of Congresses in the field, and offering Refresher Courses at recognized centers and given by recognized authorities in the several fields of Medical Radiology.

11. The Committee on Education of the Inter-American College of Radiology shall clarify any doubt or problem which may arise in the practical application of these Recommendations on the Teaching of Radiology.

The President of the Inter-American College of Radiology is Dr. Gonzalo Esguerra Gomez, Clinica de Marly, Bogotá, Colombia, and the Secretary, Dr. Mario Gaitan Yanguas, Clinica de Marly, Bogotá, Colombia.

NEWS ITEMS

GOLDEN ANNIVERSARY OF THE RADIOLOGICAL SOCIETY OF NORTH AMERICA

The recent Annual Meeting of the Radiological Society of North America, held at the Palmer House, Chicago, November 29–December 4, 1964, was its Golden Anniversary Meeting. The festive Gold covered issue of *Radiology*, its official Journal, on this occasion, appropriately expressed the impact that the Society has had on Radiology, not only in this country, but throughout the world.

Dr. Howard P. Doub, able Historian of the Society and distinguished Editor of *Radiology* for many years, in a chronologic synopsis of the salient events encompassing "Fifty Years of Progress," masterfully traced from its humble beginnings the organization which today "is believed to be the largest scientific radiological society in the world." Dr. Laurence L. Robbins, Past President, in editorializing this "proud" occasion, analyzed the "significant trends in organized radiology" which contributed, in great part, to such an impressive attainment. "There can be no question," states Dr. Robbins, "that the Radiological Society of North America has had an impact on radiology in particular and medicine in general." As the radiologic frontiers continue to expand, Dr. Robbins confidently predicts that "Its impact for the future is in the hands of its members."

THE AMERICAN JOURNAL OF ROENTGENOLOGY, RADIUM THERAPY AND NUCLEAR MEDICINE joins in the celebration of this anniversary and congratulates the Radiological Society of North America for its fifty years of progress and dedication to Radiology.

COURSE IN NEURORADIOLOGY

A couse in "Neuroradiology: Techniques and Methods of Diagnosis" will be presented by the University of California Extension, Monday and Tuesday, February 1 and 2, 1965, at UCLA.

Co-sponsored by Continuing Education in Medicine and the UCLA School of Medicine, the course immediately follows the Annual Midwinter Conference of the Los Angeles Radiological Society. It will offer the practicing radiologist an opportunity to perfect himself in the advanced techniques of roentgen diagnosis of neurologic disorders.

Motion pictures and other visual aids will be utilized to present detailed aspects of these procedures and to analyze subsequent roentgen findings.

Leo G. Rigler, M.D., Professor of Radiology, will serve as Chairman for the two day program. The Guest Faculty will be Thomas N. Newton, M.D., Assistant Professor of Radiology, University of California School of Medicine, San Francisco Medical Center and Claes Rådberg, M.D., Chief Physician, Roentgen Department II, Sahlgrenska Sjukhuset, Gothenburg, Sweden.

Further information may be obtained from Thomas H. Sternberg, Assistant Dean, Postgraduate Medical Education, UCLA Center for the Health Sciences, Los Angeles, California 90024.

POSTGRADUATE COURSE IN DIAGNOSTIC RADIOLOGY

The Eighth Annual Postgraduate Course in Diagnostic Radiology will be presented by the Department of Radiology and Continuing Education in Medicine and the Health Sciences of the University of California San Francisco Medical Center, March 10–14, 1965.

This is an intensive five day course which includes lectures, panel discussions, symposia, exhibits, and a social hour. Registrants may enroll for the full five days or by the day.

The Program Chairman is Dr. Alexander R. Margulis, Professor and Chairman, Department of Radiology, University of California School of Medicine, San Francisco; the Program Director is Dr. Howard L. Steinbach, Professor of Radiology, University of California School of Medicine, San Francisco; and the Assistant Program Director is Dr. Charles D. Noonan, Assistant Professor of Radiology, University of California School of Medicine, San Francisco.

The course will be conducted by the faculty of the Department of Radiology and the following guest speakers: David H. Baker, M.D., Columbia-Presbyterian Medical Center, New York, New York; Alfred S. Berne, M.D., State University of New York Medical Center, Syracuse, New York; Bernard S. Epstein, M.D., Albert Einstein College of Medicine, Yeshiva University, New York, New York; William R. Eyler, M.D., Henry Ford Hospital, Detroit, Michigan; Nathaniel Finby, M.D., Columbia University College of Physicians and Surgeons, New York, New York; Robert M. Lowman, M.D., Yale University School of Medicine, New Haven, Connecticut; Björn Nordenström, M.D., Thoraxkliniken, Karolinska Sjukhuset, Stockholm, Sweden; Mannie M. Schechter, M.B., B.Ch., D.M.R.D., Albert Einstein College of Medicine, Yeshiva University, New York, New York; and Basil Strickland, M.B., M.R.C.P., Westminster Hospital, London, England.

For further information please write to: Seymour M. Farber, M.D., Dean of Educational Services and Director of Continuing Education, Health Sciences, University of California Medical Center, San Francisco, California 94122.

POSTGRADUATE SEMINAR "GASTROINTESTINAL ROENTGENOLOGY"

The University of Miami School of Medicine presents Postgraduate Seminar "Gastrointestinal Roentgenology," March 17–20, 1965, at Fontainebleau Hotel, Miami Beach, Florida, with Raymond E. Parks, M.D., Professor and Chairman of Radiology, University of Miami, as Director; Manuel Viamonte, Jr., M.D., as Chairman of the Scientific Program Committee; and Robert F. Feltman, M.D., as Chairman of the Registration Committee.

The seminar will deal with new and changing concepts of gastrointestinal roentgen diagnosis. The presentations will include the esophagus, stomach, gallbladder, small intestine, colon and pancreas, in both adult and child. Two film reading pathologic conferences will be held. Each morning session of the seminar will have two general discussions, one dealing with technical aspects of gastrointestinal fluoroscopy and the other will be a question and answer session on the presentations of the morning.

The Faculty will include, in addition to members of the staff of the University School of Medicine, the following Guest Speakers: Henry L. Bockus, M.D., University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; Benjamin Felson, M.D., University of Cincinnati College of Medicine, Cincinnati, Ohio; Johan Frimann-Dahl, M.D., University of Oslo, Oslo, Norway; C. Allen Good, M.D., Mayo Clinic, Rochester, Minnesota; Elson B. Helwig, M.D., Armed Forces Institute of Pathology, Washington, D. C.; Richard H. Marshak, M.D., Mount Sinai Hospital, New York, New York; Richard Schatzki, M.D., Mount Auburn Hospital, Cambridge, Massachusetts; William B. Seaman, M.D., College of Physicians and Surgeons of Columbia University, New York, New York; Edward B. Singleton, M.D., St. Luke's and Texas Children's Hospitals, Houston, Texas; Solve Welin, M.D., Malmö Allmänna Sjukhuset, Malmö, Sweden; and Robert E. Wise, M.D., Lahey Clinic and New England Baptist Hospital, Boston, Massachusetts.

For further information please write to Department of Radiology, University of Miami School of Medicine, Jackson Memorial Hospital, Miami, Florida 33136.

The Fontainebleau Hotel will send a room reservation form to all registrants for accommodations at special rates that will apply for the period of the Seminar and one week preceding and following the Seminar.

SOCIÉTÉ EUROPÉENNE DE RADIOLOGIE PÉDIATRIQUE

The European Society for Pediatric Radiology will hold its next Annual Meeting in Stockholm, Sweden, May 20–22, 1965, with Dr. Ulf Rudhe as President, and Dr. Ole Eklöf, P. O. Box, Stockholm 60, Sweden, as General Secretary.

The Permanent Secretary of the Society is Dr. Jaques Sauvegrain, Hôpital des Enfants-Malades, 149, rue de Sèvres, Paris 15e, France.

FIRST INTERNATIONAL CONFERENCE OF MEDICAL PHYSICS

The First Conference of the International Organization for Medical Physics (I.O.M.P) will be held September 8–10, 1965 at Harrogate, England. This will be followed by visits to hospitals and research centers in the north of Great Britain on September 13, and in the south of Great Britain on September 15, excluding the London area to which visits will be made on September 17.

The main division of topics under consideration at the Conference will be: (1) Physics in Medicine and Surgery; (2) Physics Applied to Physiology; and (3) Physics in Radiology.

There will also be a technical exhibition at Harrogate and scientific exhibitions at the centers visited.

The Conference is under the patronage of Sir John Cockroft, O.M., K.C.B., C.B.E., F.R.S., with Dr. W. V. Mayneard, C.B.E., as President.

Further information and Registration forms are available from the Secretary, United Kingdom National Committee for Medical Physics, 45/47 Little Britain, London, E.C.1., England.

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THE ASSOCIATION OF UNIVERSITY RADIOLOGISTS

ANNUAL MEMORIAL MEDAL AWARD COMPETITION

An Annual Memorial Medal Award, in honor of deceased AUR members, is awarded to the resident in radiology writing the best original paper on some aspect of radiology during the period of competition. The paper must be the work of only one author, the resident. Manuscripts to be considered for the 1965 competition must be received by March 1, 1965.

Inquiries should be addressed and papers submitted to the Secretary of the AUR, Alexander R. Margulis, M.D., Department of Radiology, University of California San Francisco Medical Center, San Francisco, California 94122.

The 1965 annual meeting will be held at the University of Washington, Seattle, Washington, May 14 and 15, 1965.

BOOK REVIEW

Books sent for review are acknowledged under: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interest of our readers as space permits.

DIAGNOSTIC NEURORADIOLOGY. By Juan M. Taveras, M.D., Professor of Radiology, College of Physicians and Surgeons, Columbia University; Attending Radiologist, Neurological Institute, Presbyterian Hospital of New York; and Ernest H. Wood, M.D., Professor and Chairman, Department of Radiology, School of Medicine, University of North Carolina; Director of Radiological Service, North Carolina Memorial Hospital; Formerly Attending Radiologist, Neurological Institute, Presbyterian Hospital of New York. Cloth. Pp. 1,960, with 722 illustrations. Price, $32.50. The Williams & Wilkins Co., 428 East Preston Street, Baltimore, Md., 1964.

This is an outstanding work. It will be the standard against which all English language writing on neuroradiology will be compared for years. It is detailed and complete. The authors have presented the different points of view on the controversial topics but have also made clear their personal beliefs. It is a very practical book, full of mature observations that are seldom found in print. Of particular value are the sections on increased intracranial pressure, intracranial calcifications, intracranial pneumography and the section on selection of diagnostic procedure. In this latter section, there is some mention of ultrasonic echography and external isotope localization.

The arrangement follows the classical pattern, chapters on the skull being followed by sections on intracranial pneumography, angiography, selection of diagnostic procedures, head injuries and their complications and, finally, diseases of the spinal cord.

In such a large and valuable work, criticism is apt to reflect the interests or bias of the observer but this should not detract from the work being reviewed. For example, in the section "Platybasia," the author states "in practice platybasia has come to indicate the group of abnormalities encountered in the region of the foramen magnum. . . . " Such over-simplification is a retrograde step. These abnormalities consist of several different acquired and various congenital lesions of different significance, requiring different forms of treatment. In certain places the nomenclature might be misleading. For example, the angiographic sylvian point is apt to be mistaken for the anatomists' sylvian point, yet they are different points; and attributing the impressions on the top of the skull to pacchionian granulations when many of them are due to venous lacunae in the dura mater (lacunae laterales).

The absence of the word "epilepsy" from the table of contents is perhaps understandable but may exasperate some persons trying to use the book. The most important defect is the lack of a classified index and it is only partly remedied by a moderately detailed table of contents. Its page numbering is clumsy but is perhaps inevitable in a book which is also a section of a loose-leaf system, "Golden's Diagnostic Radiology."

This book, of course, is directed to radiologists, neurologists and neurosurgeons and should be considered required reading for them. It is essential to every hospital in which neuroradiological procedures are being carried out. In hospitals or offices in which neuroradiological procedures are not performed, its sections on skull and spinal cord make it most valuable.

DONALD MCRAE, M.D.

BOOKS RECEIVED

POLYPOID LESIONS OF THE GASTROINTESTINAL TRACT. By Claude E. Welch, M.D., Visiting Surgeon, Massachusetts General Hospital, Boston; Clinical Professor of Surgery, Harvard Medical School, Boston. Volume II in Series "Major Problems in Clinical Surgery," J. Englebert Dunphy, M.D., Consulting Editor. Cloth. Pp. 148, with many illustrations. Price, $7.50. W. B. Saunders Company, Philadelphia, Pa., 1964.

COPPER AND PEROXIDES IN RADIOBIOLOGY AND MEDICINE. By Jack Schubert, Ph.D., Associate Technical Director, Nuclear Science and Engineering Corporation, Pittsburgh, Pa. Cloth. Pp. 217, with many tables. Price, $9.00. Charles C Thomas, Publisher, 301–327 East Lawrence Avenue, Springfield, Ill., 1964.

Bone Biodynamics. Henry Ford Hospital International Symposium. Edited by Harold M. Frost, M.D., Director, Orthopaedic Research Laboratory; Associate Surgeon, Department of Orthopaedic Surgery, Henry Ford Hospital, Detroit, Mich. Cloth. Pp. 704, with 211 illustrations. Price, $18.00. Little, Brown and Company, Boston, Mass. 02106, 1964.

Scintillation Scanning in Clinical Medicine. Based on a Symposium Sponsored by the Department of Radiology of the Bowman Gray School of Medicine. Edited by James L. Quinn, III, M.D., Assistant Professor of Radiology, Northwestern University School of Medicine; Director of Nuclear Medicine, Chicago Wesley Memorial Hospital; Formerly Chief, Nuclear Medicine Service, The Bowman Gray School of Medicine. Cloth. Pp. 278, with many illustrations. Price, $11.50. W. B. Saunders Company, Philadelphia, Pa., 1964.

Cobalt-60 Teletherapy. A Handbook for the Radiation Therapist and Physicist. By Ivan H. Smith, M.D., M.Sc., F.R.C.S. (Edin.), F.I.C.S., F.A.C.R., Professor and Head of the Department of Therapeutic Radiology, and Lecturer in Pathology, University of Western Ontario; Director, Ontario Cancer Foundation, London Clinic, London, Ont. (Deceased); J. C. M. Fetterly, M.D., C.M., D.M.R.T. (Eng.), Associate Professor of Radiology, University of Western Ontario; Director, Ontario Cancer Foundation, London Clinic, London, Ont.; J. S. Lott, B.A., M.D., D.M.R.T. (Eng.), Associate Professor of Radiology, Director of Division of Radiotherapy, The Johns Hopkins Medical School and Hospital, Baltimore, Md.; Formerly Senior Radiotherapist, Ontario Cancer Foundation, London Clinic, London, Ont.; J. C. F. MacDonald, M.A., Ph.D., Assistant Professor of Therapeutic Radiology, Honorary Lecturer in Physics, University of Western Ontario; Senior Physicist, Ontario Cancer Foundation, London Clinic, London, Ont.; Lois M. Myers, B.A., M.D., Ph.D., D.M.R.T. (Eng.), Lecturer in Therapeutic Radiology, University of Western Ontario; Radiotherapist, Ontario Cancer Foundation, London Clinic, London, Ont.; P. M. Pfalzner, B.A., M.Sc., Lecturer in Therapeutic Radiology, University of Western Ontario; Physicist, Ontario Cancer Foundation, London Clinic, London, Ont.; and D. L. Thomson, M.B., Ch.B., D.M.R.T. (Eng.), Clinical Associate Professor, Therapeutic Radiology, University of Western Ontario; Senior Radiotherapist, Ontario Cancer Foundation, London Clinic, London, Ont., Canada. Cloth. Pp. 464, with many illustrations. Price, $18.50. Hoeber Medical Division, Harper & Row, Publishers, 49 East 33rd Street, New York 16, N. Y., 1964.

Respiratory Function in Disease. An Introduction to the Integrated Study of the Lung. By David V. Bates, M.D. (Cantab.), M.R.C.P. (London), Associate Professor of Medicine, McGill University; Director, Respiratory Division, Joint Cardiorespiratory Service, Royal Victoria Hospital, and Montreal Children's Hospital; and Ronald V. Christie, M.D. (Edinburgh), M.Sc. (McGill), D.Sc. (London), Sc.D. (Dublin), F.A.C.P., F.R.C.P. (London), F.R.C.P.(C), Professor and Chairman of Department of Medicine, McGill University; Physician-in-Chief, Royal Victoria Hospital, Montreal, Que., Canada. Cloth. Pp. 566, with some illustrations. Price, $15.50. W. B. Saunders Company, Philadelphia, Pa., 1964.

Experience in Renal Transplantation. By Thomas E. Starzl, Ph.D., M.D., Professor of Surgery, University of Colorado School of Medicine; Chief, Surgical Service, Veterans Administration Hospital, Denver, Colo. Cloth. Pp. 383, with many illustrations. Price, $17.00. W. B. Saunders Company, Philadelphia, Pa., 1964.

Genetics and Man. By C. D. Darlington, F.R.S., Magdalen College, Oxford, England. A revised and expanded edition of "The Facts of Life," published in 1953. Cloth. Pp. 382, with some illustrations. Price, $7.50. The Macmillan Company, 60 Fifth Avenue, New York 11, N. Y., 1964.

Mammography. By Robert L. Egan, M.D., Associate Radiologist, The Methodist Hospital of Indiana, Indianapolis, Ind.; Consultant Cancer Control Program, Division of Chronic Diseases, Department of Health, Education and Welfare; Consultant Health Insurance Plan of New York City Mammography Study; Consultant Glen Cove Community Hospital, Glen Cove, Long Island, N. Y.; Formerly, Associate Professor of Radiology, Head of Section of Experimental Diagnostic Radiology, The University of Texas M. D. Anderson Hospital and Tumor Institute, Houston, Texas. Cloth. Pp. 446, with 302 illustrations. Price, $25.50. Charles C Thomas, Publisher, 301–327 East Lawrence Avenue, Springfield, Ill., 1964.

Atomic Medicine. Edited by Charles F. Behrens, M.D., F.A.C.R., Rear Admiral MC, U. S. Navy, (ret.); Roentgenologist, Yater Clinic, Washington, D. C.; Consultant and Lecturer in Radiology, U. S. Naval Medical Center, Bethesda, Md.; Formerly, Director, Atomic Defense Division, Bureau of Medicine and Surgery, Navy Department; Commanding Officer, Navy Medical Research Institute, National Naval Medical Center, Bethesda, Md.; and E. Richard King, M.D., Captain, MC, U. S. Navy (ret.); Professor and Chairman of Division of Radiation Therapy and Nuclear Medicine, Department of Radiology, Medical College of Virginia; Formerly, Chief of Radiology, U. S. Naval Hospital, Bethesda, Md. Cloth. Pp. 766, with some illustrations. Price, $18.00. The Williams & Wilkins Company, Baltimore 2, Md., 1964.

THE OBSTRUCTING ACROMION. UNDERLYING DISEASE, CLINICAL DEVELOPMENT, AND SURGERY. By Bernard Diamond, M.D., F.A.C.S., D.O.B. Orthopaedic Surgery, Fellow International College of Surgeons. Cloth. Pp. 212, with 97 illustrations. Price, $9.50. Charles C Thomas, Publisher, 301–327 East Lawrence Avenue, Springfield, Ill., 1964.

CANCER RATES AND RISKS. By John C. Bailar, III, M.D., Haitung King, Ph.D., and Marie Joy Mason, M.D., Demography Section of the Biometry Branch, National Cancer Institute. Public Health Service Publication No. 1148. Paper. Pp. 93, with many tables. Price, $0.40. Superintendent of Documents, U. S. Government Printing Office, Washington, D. C. 20402, 1964.

END RESULTS IN CANCER. REPORT No. 2. Prepared for The End Results Group by the Clinical Biometry Section, National Cancer Institute. Public Health Service Publication No. 1149. Paper. Pp. 122, with many tables and graphs. Price, $0.75. U. S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, Bethesda, Md. 20014. For sale by the Superintendent of Documents, U. S. Government Printing Office, Washington, D. C. 20402, 1964.

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SOCIETY PROCEEDINGS

MEETINGS OF RADIOLOGICAL SOCIETIES*

United States of America

American Roentgen Ray Society
Secretary, Dr. C. Allen Good, Mayo Clinic, Rochester, Minn. Annual meeting: Hilton Hotel, Washington, D. C., Sept. 28–Oct. 1, 1965.

American Radium Society
Secretary, Dr. John L. Pool, 444 East 68th Street, New York, N. Y. 10021. Annual meeting: Roosevelt Hotel, New Orleans, La., April 8–10, 1965.

Radiological Society of North America
Secretary-Treasurer, Dr. Maurice Doyle Frazer, 1744 South Fifty-eighth St., Lincoln, Neb. Annual meeting to be announced.

American College of Radiology
Executive Director, William C. Stronach, 20 N. Wacker Drive, Chicago 6, Ill. Annual meeting: Bellvue Stratford Hotel, Philadelphia, Pa., Feb. 10–13, 1965.

Section on Radiology, American Medical Association
Secretary, Dr. Clyde A. Stevenson, Sacred Heart Hospital, West 101 Eight Ave., Spokane 4, Wash. Annual meeting: New York, N. Y., June 20–24, 1965.

American Board of Radiology
Secretary, Dr. H. Dabney Kerr. Correspondence should be directed to Kahler Hotel Building, Rochester, Minn.

The Spring 1965 examination will be held at the San Francisco Hilton Hotel, San Francisco, Calif., June 13–18, inclusive. This will be the last time that the Special Examination in Nuclear Medicine will be offered to physicians who are already certified in Radiology or Therapeutic Radiology. The deadline for filing applications for this examination was December 31, 1964.

The Fall 1965 examination will be held at the Statler Hilton Hotel, Dallas, Texas, December 5–10, inclusive. The deadline for filing applications for this examination is June 30, 1965.

American Association of Physicists in Medicine
Secretary-Treasurer, Charles S. Simons, University of Michigan Hospital, Ann Arbor, Mich. Annual meeting to be announced.

American Club of Therapeutic Radiologists
Secretary, Dr. J. A. del Regato, Penrose Cancer Hospital, Colorado Springs, Colo.

Eleventh International Congress of Radiology
Secretary-General, Professor Dr. Med. Arduino Ratti, via Moscova, 44-1, Milan, Italy. Address inquiries to Professor Dr. Med. Luigi Turano, President-Elect, Istituto di Radiologia, Università di Roma, Rome, Italy. Meeting: September 22–28, 1965.

Ninth Inter-American Congress of Radiology
Counselor for the United States, Dr. Philip J. Hodes, Jefferson Medical College Hospital, 11th and Walnut Streets, Philadelphia 7, Pennsylvania. Meeting: Montevideo, Uruguay, 1967.

Alabama Radiological Society
Secretary, Dr. Walter Brower, Birmingham, Ala. Meets time and place of Alabama State Medical Association.

American Nuclear Society
Treasurer, Raymond Maxson, 86 E. Randolph St., Chicago, Ill. Annual meeting to be announced.

Arizona Radiological Society
Secretary-Treasurer, Dr. George Gentner, 3435 W. Durango, Phoenix, Ariz. Two regular meetings a year. Annual meeting at time and place of State Medical Association and interim meeting six months later.

Arkansas Radiological Society
Secretary, Dr. Charles W. Anderson, 1108½ Poplar, Pine Bluff, Ark. Meets every three months and also at time and place of State Medical Association.

Association of University Radiologists
Secretary-Treasurer, Dr. Alexander R. Margulis, Department of Radiology, University of California, San Francisco, Calif. Annual meeting: Seattle, Washington, May 14 and 15, 1965.

Atlanta Radiological Society
Secretary, Dr. Donald R. Rooney, Burnt Hickory Road, Marietta, Ga. Meets monthly except during three summer months, on third Tuesday, at the Academy of Medicine, Atlanta, Ga., at 8:00 P.M.

Bavarian-American Radiologic Society
Secretary, Dr. Roy R. Deffebach, Major, MC, Radiology Service, 5th General Hospital, APO 154, New York, N. Y. Meets quarterly.

Blockley Radiological Society
Secretary, Dr. Bernard J. Ostrum, 2412 North 52nd St., Philadelphia, Pa.

Bluegrass Radiological Society
Secretary-Treasurer, Dr. Daniel J. Hanson, University of Kentucky, Medical Center, Lexington, Kentucky. Meets quarterly.

Brooklyn Radiological Society
Secretary, Dr. Jay P. Sackler, Brooklyn, N. Y. Meets first Thursday of each month, October through June.

Buffalo Radiological Society
Secretary, Dr. Berkeley Zinn, 85 Wehrle Dr., Buffalo 25, N. Y. Meets second Monday evening each month, October to May inclusive.

California Radiological Society
Secretary, Dr. L. Henry Garland, Suite 1739, 450 Sutter St., San Francisco, Calif. Meets annually during meeting of California Medical Association.

Catawba Valley Radiological Society
Secretary, Dr. Emmett R. White, P. O. Box 303, Rutherford College, N. C. Meets every Tuesday, Dept. of Radiology, Valdese General Hosp., Valdese, N. C. at 12:00 P.M.

Central New York Radiological Society
Secretary-Treasurer, Dr. Edward W. Carsky, Crouse-Irving Hospital, 820 S. Crouse Ave., Syracuse, N. Y. Meets first Monday each month, October through May.

Central Ohio Radiological Society
Secretary-Treasurer, Dr. Harold W. Long, 81 S. Fifth St., Columbus 15, Ohio. Meets third Thursday in October, and second Thursday in November, January, March and May at Fort Hayes Hotel, Columbus, Ohio.

Central Society of Nuclear Medicine
Secretary, Dr. Robert S. Landauer, Radiation Center Bldg., 1903 West Harrison St., Chicago 12, Ill.

Chicago Roentgen Society
Secretary-Treasurer, Dr. Robert D. Moseley, Jr., Dept. of Radiology, Univ. of Chicago, 950 E. 59th St., Chicago 37, Ill. Meets second Thursday of each month, October to April except December at the Pick-Congress Hotel at 8:00 P.M.

Cleveland Radiological Society
Secretary-Treasurer, Dr. James Christie, 10515 Carnegie Avenue, Cleveland, Ohio. Meetings at 7:00 P.M. on fourth Monday of October, November, January, February, March and April.

Colorado Radiological Society
Secretary, Dr. David J. Stephenson, 8300 West 38th Ave., Wheat Ridge, Colo. Meets third Friday of each month at Denver Athletic Club from September through May.

*** Secretaries of societies are requested to send timely information promptly to the Editor.**

Connecticut Valley Radiologic Society
Secretary, Dr. William W. Walthall, Jr., 137 Maple St., Hartford 6, Conn. Meets in April and October.

Dallas-Fort Worth Radiological Society
Secretary, Dr. Paul W. Mathews, Jr., 1217 West Cannon St., Fort Worth, Tex. Meets monthly, third Monday, at Southwest International Airport at 6:00 P.M.

Detroit Roentgen Ray and Radium Society
Secretary, Dr. Arch H. Hall, Harper Hospital, Detroit 1, Mich. Meets monthly, first Thursday, October through May, at David Whitney House, 1010 Antietam, at 6:30 P.M.

East Bay Roentgen Society
Secretary, Dr. Dan Tucker, 434 30th St., Oakland 9, Calif. Meets first Thursday each month at Peralta Hospital, Oakland, Calif.

East Tennessee Radiological Society
Secretary, Dr. C. H. Kimball, 2200 Harris Circle, Cleveland, Tenn. Meets in January and September.

Eastern Radiological Society
Secretary, Dr. James F. Martin, North Carolina Baptist Hospital, Winston-Salem, N. C.

Florida Radiological Society
Secretary, Dr. Andre S. Capri, 3471 N. Federal Highway, Fort Lauderdale, Fla. Meets twice annually, in the spring with the annual State Society Meeting and in the fall.

Florida West Coast Radiological Society
Secretary-Treasurer, Dr. Garth R. Drewry, Tampa General Hospital, Tampa 6, Fla. Meets in January, April, July and October.

Georgia Radiological Society
Secretary, Dr. David Robinson, P. O. Box 394, Savannah, Ga. Meets in spring and fall with Annual State Society Meeting.

Greater Miami Radiological Society
Secretary-Treasurer, Dr. Oliver P. Winslow, Jr., Baptist Hospital of Miami, Inc., 8900 S. W. 88th St., Miami 56, Fla. Meets monthly, third Wednesday at 8:00 P.M. at Jackson Memorial Hospital, Miami, Fla.

Greater St. Louis Society of Radiologists
Secretary, Dr. C. M. Witt, #16 Hampton Village Plaza, St. Louis 9, Mo.

Houston Radiological Society
Secretary, Dr. D. A. Van Velzer, Texas Medical Center Library, Jesse H. Jones Library Bldg., Houston 25, Tex. Meets fourth Monday of each month, except June, July, August and December, at the Doctors' Club, 8:00 P.M., Houston, Tex.

Idaho State Radiological Society
Secretary, Dr. George H. Harris, Bannock Memorial Hospital, Pocatello, Idaho. Meets in the spring and fall.

Illinois Radiological Society
Secretary, Dr. George A. Miller, Carle Hospital Clinic, Urbana, Ill. Meets in the spring and fall.

Indiana Roentgen Society, Inc.
Secretary, Dr. Richard A. Silver, 1815 N. Capitol Avenue, Indianapolis, Ind. Meets first Sunday in May and during fall meeting of Indiana State Medical Association.

Iowa Radiological Society
Secretary, Dr. L. L. Maher, 1419 Woodland Ave., Des Moines, Iowa. Luncheon and business meeting during annual session of Iowa State Medical Society. The scientific section is held in the autumn.

Kansas Radiological Society
Secretary-Treasurer, Dr. R. F. Conrad, Newman Memorial Hosp., Emporia, Kan. Meets in spring with State Medical Society and in winter on call.

Kentucky Radiological Society
Secretary-Treasurer, Dr. Joan R. Hale, 402 Heyburn Building, Louisville, Ky. Meets monthly on second Friday at Sheraton Hotel, Louisville, Ky.

Kings County Radiological Society
Secretary, Dr. Stanley Dannenberg, 1917 Bedford Ave., Brooklyn 25, N. Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:45 P.M.

Knoxville Radiological Society
Secretary, Dr. Clifford L. Walton, Blount Professional Bldg., Knoxville 20, Tenn. Meetings are held the third Monday of every other month at the University of Tennessee Memorial Research Center and Hospital.

Los Angeles Radiological Society
Secretary, Dr. Austin R. Wilson, 540 N. Central Ave., Glendale, Calif. 91203. Meets second Wednesday of month in November, January, April and June at Los Angeles County Medical Association Building, Los Angeles, Calif. Annual midwinter meeting: Biltmore Hotel, Los Angeles, Calif., Jan. 30–31, 1965.

Maine Radiological Society
Secretary, Dr. J. T. Chen, 7 Cherry Hill Terrace, Waterville, Me. Meets in June, September, December and April.

Maryland Radiological Society
Secretary, Dr. Henry Startzman, Medical Arts Building, Baltimore, Maryland.

Memphis Roentgen Society
Secretary-Treasurer, Dr. Irving K. Ettman, 684 W. Brookhaven Circle, Memphis, Tenn. Meets first Monday of each month at John Gaston Hospital.

Miami Valley Radiological Society
Secretary, Dr. William D. Roberts, 2197 Los Arrow Dr., Dayton 9, Ohio. Meets second Friday of fall and winter months.

Mid-Hudson Radiological Society
Secretary-Treasurer, Dr. Alexander W. Friedman, Mid-Hudson Medical Group, Fishkill, N. Y. Meets 7:00 P.M., first Wednesday of each month September to May.

Milwaukee Roentgen Ray Society
Secretary-Treasurer, Dr. Harold F. Ibach, 2400 W. Villard Avenue, Milwaukee 9, Wis. Meets monthly on fourth Monday, October through May, at University Club.

Minnesota Radiological Society
Secretary-Treasurer, Dr. Frank J. Anderson, 810 E. 27th St., Minneapolis 7, Minn. Meets three times annually, in fall, winter and spring.

Mississippi Radiological Society
Secretary-Treasurer, Dr. Dan T. Keel, Jr., 504 Chippewa St., Brookhaven, Miss. Meets third Thursday of each month at the Heidelberg Hotel, Jackson, at 6:00 P.M.

Missouri Radiological Society
Secretary-Treasurer, Dr. M. Shoss, Cape Girardeau, Mo.

Montana Radiological Society
Secretary, Dr. Clark Grimm, Great Falls, Montana. Meets at least once a year.

Nassau Radiological Society
Secretary, Dr. Perry R. Mandel, Nassau Hospital, Mineola, L. I., N. Y. Meets second Tuesday of the month in February, April, June, October and December.

Nebraska State Radiological Society
Secretary, Dr. Richard Bunting, The Radiologic Center, Nebraska Methodist Hospital, Omaha 31, Neb. Meets third Wendnesday of each month at 6 P.M. in Omaha or Lincoln.

Nevada Radiological Society
Secretary, Dr. William G. Arbonies, Department of Radiology, St. Mary's Hospital, Reno, Nev.

New England Roentgen Ray Society
Secretary, Dr. Jack R. Dreyfuss, Zero Emerson Place, Boston, Mass. 02114. Meets third Friday of each month, October through April, at The Longwood Towers, 20 Chapel Street, Brookline, Mass., at 4:30 P.M.

New Hampshire Roentgen Ray Society
Secretary, Dr. Paul Y. Hasserjian, 1470 Elm St., Manchester, N. H. Meets four to six times yearly.

New Mexico Association of Radiologists
Secretary-Treasurer, Dr. Justin J. Wolfson, Department of Radiology, Bernalillo County-Indian Hospital, Albuquerque, New Mexico.

New Mexico Society of Radiologists
Secretary, Dr. William G. McPheron, Hobbs, New Mexico. Four annual meetings, three held in Albuquerque, N. M., and one held at time and place of New Mexico State Medical Society annual meeting.

New York Roentgen Society
Secretary, Dr. Harry Z. Mellins. Meets monthly on third

Monday at the New York Academy of Medicine at 4:30 P.M. Annual Spring Conference: Waldorf-Astoria Hotel, April 29, 30 and May 1, 1965.

North Carolina Radiological Society
Secretary, Dr. E. H. Schultz, North Carolina Memorial Hospital, Chapel Hill, N. C. Meets in the spring and fall each year.

North Dakota Radiological Society
Secretary, Dr. John Jestadt, Depuy-Sorkness Clinic, Jamestown, N. D. Meets at time of State Medical Association meeting. Other meetings arranged on call of the President.

North Florida Radiological Society
Secretary, Dr. Charles H. Newell, 800 Miami Road, Jacksonville 7, Fla. Meets quarterly in March, June, September and December.

Northeastern New York Radiological Society
Secretary, Dr. Anthony J. Tabacco, 621 Central Ave., Albany 6, N. Y. Meets in Albany area on second Wednesday of October, November, March and April.

Northern California Radiological Society
Secretary, Dr. John M. Johannessen, Mercy Hospital, Sacramento, Calif. Meets fourth Monday of Sept., Nov., Jan., March and May at the Sutter Club in Sacramento.

Northwestern Ohio Radiological Society
Secretary, Dr. Vito J. Zupa, Mercy Hospital, Department of Radiology, Toledo, Ohio.

Ohio State Radiological Society
Secretary, Dr. M. M. Thompson, Jr., 316 Michigan St., Toledo 2, Ohio. Annual meeting: Terrace Hilton Hotel, Cincinnati, Ohio, May, 1965.

Oklahoma State Radiological Society
Secretary, Dr. Dave B. Lhevine, 810 Doctors Bldg., 2021 South Lewis, Tulsa, Okla. Meets in January, May and October.

Orange County Radiological Society
Secretary-Treasurer, Dr. Robert M. Sodaro, 600 E. Washington Ave., Santa Ana, Calif. Meets fourth Tuesday of month except June, July, August and December in Orange County Medical Association Building.

Oregon Radiological Society
Secretary-Treasurer, Dr. James A. Schneider, St. Vincent Hospital, Portland 10, Ore. Meets on second Wednesday of month at 7:00 P.M. at the University Club, Portland, Ore.

Orleans Parish Radiological Society
Secretary, Dr. Joseph V. Schlosser, Charity Hospital, New Orleans 13, La. Meets second Tuesday of each month.

Pacific Northwest Radiological Society
Secretary, Dr. Willis Taylor, Seattle, Washington. Annual meeting to be announced.

Pennsylvania Radiological Society
Secretary-Treasurer, Dr. Frederick R. Gilmore, Clearfield Hospital, Clearfield, Pa. Annual meeting: Pittsburgh Hilton Hotel, May 21–22, 1965.

Philadelphia Roentgen Ray Society
Secretary, Dr. Antolin Raventos, Hospital of the University of Pennsylvania, Philadelphia 4, Pa. Meets first Thursday of each month at 5 P.M., from October to May in Thompson Hall, College of Physicians.

Pittsburgh Roentgen Society
Secretary, Dr. Robert N. Berk, 3305 Fifth Ave., Pittsburgh 13, Pa. Meets second Wednesday of month, October through June at Park Schenely Restaurant.

Radiological Society of Connecticut
Secretary-Treasurer, Dr. Orlando F. Gabriele, 1450 Chapel St., New Haven 11, Conn. Meetings are held bimonthly.

Radiological Society of Greater Cincinnati
Secretary, Dr. John F. Popkin, Jr., 831 Carew Tower, Cincinnati, Ohio. Meets first Monday of each month at Cincinnati Academy of Medicine.

Radiological Society of Greater Kansas City
Secretary, Dr. J. Stewart Whitmore, 1010 Rialto Bldg., Kansas City, Mo. Meets last Friday of each month.

Radiological Society of Hawaii
Secretary, Dr. Russell E. Graf, P.O. Box 294, USA Tripler General Hospital, Honolulu, Hawaii. Meets third Monday of each month at 7:30 P.M.

Radiological Society of Kansas City
Secretary, Dr. Arthur B. Smith, 800 Argyle Bldg., Kansas City, Mo. Meets third Thursday of each month.

Radiological Society of Louisiana
Secretary, Dr. Andrew F. Giesen, Ochsner Clinic, New Orleans 15, La. Meets annually during Lousiana State Medical Society meeting.

Radiological Society of New Jersey
Secretary, Dr. E. Arthur Kratzman, 912 Prospect Ave., Plainfield, N. J. Meets in Atlantic City at time of State Medical Society meeting and in October or November in Newark, N. J.

Radiological Society of the State of New York
Secretary-Treasurer, Dr. John W. Colgan, 273 Hollywood Ave., Rochester 18, N. Y. Annual meeting to be announced.

Radiological Society of South Dakota
Secretary-Treasurer, Dr. Donald J. Peik, 303 S. Minnesota Ave., Sioux Falls, S. D.

Radiological Society of Southern California
Secretary-Treasurer, Dr. John L. Gwinn, Children's Hospital of Los Angeles, 4614 Sunset Blvd., Los Angeles, Calif. 90027. Meets three times a year, usually October, February, and May.

Redwood Empire Radiological Society
Secretary, Dr. Lee F. Titus, 164 W. Napa St., Sonoma, Calif. Meets second Monday every other month.

Richmond County Radiological Society
Secretary, Dr. W. F. Hamilton, Jr., University Hospital, Augusta, Ga. Meets first Thursday of each month at various hospitals.

Rochester Roentgen Ray Society, Rochester, N. Y.
Secretary, Dr. Gerald R. Holzwasser, Rochester General Hospital, Northside Division, 1425 Portland Ave., Rochester 21, N. Y. Meets at 8:15 P.M. on the last Monday of each month, September through May, at Strong Memorial Hospital.

Rocky Mountain Radiological Society
Secretary, Dr. John H. Freed, 4200 East Ninth Ave., Denver 20, Colo. Annual meeting to be announced.

San Antonio-Military Radiological Society
Secretary, Dr. Hugho F. Elmendorf, Jr., 730 Medical Arts Bldg., San Antonio 5, Tex. Meets third Wednesday each month in Fort Sam Houston Officer's Club at 6:30 P.M.

San Diego Radiological Society
President-Secretary, Charles P. Hyslop, 7901 Frost St., San Diego 22, Calif. Meets first Wednesday of each month at the University Club.

San Francisco Radiological Society
Secretary, Dr. Malcolm Jones, University of California Hospital, San Francisco 22, Calif. Meets quarterly at the San Francisco Medical Society, 250 Masonic Ave., San Francisco 18, Calif.

Section on Radiology, California Medical Association
Secretary, Dr. William H. Graham, 630 East Santa Clara St., San Jose, Calif.

Section on Radiology, Medical Society of the District of Columbia
Secretary-Treasurer, Dr. Martin A. Thomas, 1150 Connecticut Ave., Washington 36, D. C. Meets at Medical Society Library, third Wednesday of January, March, May and October at 8:00 P.M.

Section on Radiology, Southern Medical Association
Secretary,* Dr. John D. Reeves, Department of Radiology, Univ. of Florida College of Medicine, Gainesville, Fla. Annual meeting to be announced.

Section on Radiology, Texas Medical Association
Secretary, Dr. George F. Crawford, St. Elizabeth Hospital, Beaumont, Tex. Meets annually with the Texas Medical Association.

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* Deceased.

Shreveport Radiological Club
Secretary, W. R. Harwell, 608 Travis St., Shreveport, La. Meets monthly on third Wednesday at 7:30 P.M., September to May inclusive.

Society for Pediatric Radiology
Secretary, Dr. John L. Gwinn, Children's Hospital, Los Angeles 27, Calif. Annual meeting: Hilton Hotel, Washington, D. C., Sept. 27, 1965.

Society of Nuclear Medicine
Secretary, Mr. C. Craig Harris, Oak Ridge National Laboratories, Oak Ridge, Tenn. *Administrator*, Mr. Samuel N. Turiel, 430 N. Michigan Ave., Chicago 11, Ill. Annual meeting: Bal Harbour, Fla., June 16–19, 1965.

South Bay Radiological Society
Secretary, Northern Section: Dr. John H. Callaghan, 2900 Whipple Ave., Redwood City, Calif.; Southern Section: Dr. Paul L. Clemetson, 877 W. Fremont Ave., Suite C-3, Sunnyvale, Calif. Meets second Wednesday of each month.

South Carolina Radiological Society
Secretary, Dr. George W. Brunson, 1406 Gregg St., Columbia, S. C. Annual meeting (primarily business) in conjunction with the South Carolina Medical Association meeting in May. Annual fall scientific meeting at time and place designated by the president.

South Dakota Radiological Society
Secretary, Dr. Donald J. Peik, 1417 S. Minnesota Ave., Sioux Falls, S. Dak. Meets in spring with State Medical Society and in fall.

Southern Radiological Conference
Secretary-Treasurer, Dr. Marshall Eskridge, Mobile Infirmary, P.O. Box 4097, Mobile, Ala. Annual meeting: Grand Hotel, Point Clear, Ala., Jan. 29–31, 1965.

Southwestern Radiological Society
Secretary, John M. McGuire, 904 Chelsea, El Paso, Tex. Meets last Monday of each month at 6:30 P.M. in the Paso del Norte Hotel.

Tennessee Radiological Society
Secretary, Dr. B. M. Brady, St. Joseph Hospital, Memphis, Tenn. Meets annually at the time and place of the Tennessee State Medical Association meeting.

Texas Radiological Society
Secretary, Dr. R. P. O'Bannon, 402 Professional Bldg., 1216 Pennsylvania Ave., Fort Worth 4, Tex. Annual meeting: Houston, Texas, Jan. 29–30, 1965.

Tri-State Radiological Society
Secretary, Dr. John H. Marchand, Jr., Methodist Hospital, Henderson, Ky. Meets third Wednesday of Oct., Jan., March and May, 8:00 P.M., Elks Club in Evansville, Ind.

University of Michigan Department of Roentgenology Staff Meeting
Meets each Monday evening from September to June, at 7:00 P.M. at University Hospital, Ann Arbor, Mich.

Upper Peninsula Radiological Society
Secretary, Dr. A. Gonty, Menominee, Mich. Meets quarterly.

Utah State Radiological Society
Secretary, Dr. Carlisle C. Smith, Salt Lake General Hospital, Salt Lake City, Utah. Meets fourth Wednesday in January, March, May, September and November at Holy Cross Hospital.

Vermont Radiological Society
Secretary, Dr. John R. Williams, 160 Allen St., Rutland, Vt.

Virginia Radiological Society
Secretary, Dr. John M. Ratliff, Mary Immaculate Hospital, Newport News, Va.

Washington State Radiological Society
Secretary, Dr. Owen Marten, 930 Terry Avenue, Seattle, Wash. Meets quarterly.

West Virginia Radiological Society
Secretary, Dr. Karl J. Myers, The Myers Clinic-Broaddus Hospital, Philippi, W. Va. Meets concurrently with Annual Meeting of West Virginia State Medical Society; other meetings arranged by program committee.

Westchester Radiological Society
Secretary, Dr. Joel J. Schwartzman, Westchester Academy of Medicine, Section on Radiology, Purchase, N. Y. Meets on third Tuesday of January and October and on two other dates.

Wisconsin Radiological Society
Secretary, Dr. Charles Benkendorf, 408 St. Francis St., Green Bay, Wis. Meets twice a year, May and September.

Cuba, Mexico, Puerto Rico and Central America

Asociación de Radiólogos de Centro America y Panamá. Comprising: Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica and Panamá.
Secretary-General, Dr. Raul Arguello, 5a. Ave., Norte No. 48, San Salvador, El Salvador. Meets annually in a rotating manner in the six countries.

Sociedad de Radiología de El Salvador
Secretary, Dr. Rafael Vaga Gómez.

Sociedad de Radiología de Guatemala
Secretary, Dr. Carlos E. Escobar, 9ª. Calle A 0-05, Zona 1, Guatemala.

Sociedad de Radiología y Fisioterapía Cubana
Secretary, Dr. Miguel A. García Plasencia, Hospital Curie, 29 y F, Vedado, Habana, Cuba. Meets monthly at Curie Hospital.

Sociedad Costarricense de Radiologia
Secretary, Dr. James Fernández Carballo, Apartado VIII, San José, Costa Rica.

Sociedad Mexicana de Radiología, A.C.
Calle del Oro No. 15, México 7, D. F.
Secretary-General, Dr. E. Alvarez Hernández.
Meets first Monday of each month.

Asociación Puertorriqueña de Radiología
Secretary, Dr. R. B. Díaz Bonnet, Suite 504, Professional Bldg., Santurce, Puerto Rico.

Sociedad Radiológica Panameña
Secretary, Dr. L. Arrieta Sánchez, Apartado No. 6323, Panamá, R. de P. Meets monthly in a department of radiology of a local hospital chosen at preceding meeting.

Sociedad Radiológica de Puerto Rico
Secretary, Dr. Jorge Carreras Girard, Suite 504, Professional Bldg., Santurce, Puerto Rico. Meets second Thursday of each month at 8:00 P.M. at the Puerto Rico Medical Association Bldg. in San Juan.

British Commonwealth of Nations

Association of Radiologists of the Province of Quebec
Secretary, Dr. R. Robillard, Notre-Dame Hospital, 1560 Sherbrooke St., East, Montreal, Que., Canada. Meets four times a year.

British Institute of Radiology
Honorary Secretary, Dr. R. D. Hoare, 32 Welbeck St., London, W. 1, England. Meets monthly from October until May.

Canadian Association of Physicists, Division of Medical and Biological Physics.
Honorary Secretary-Treasurer, Paul M. Pfalzner, Dept. of Therapeutic Radiology, University of Western Ontario, London, Ont., Canada. Annual meeting: Toronto, Ontario, Feb., 1965.

Edmonton and District Radiological Society
Secretary, Dr. J. T. Mason, 540 Tegler Bldg., Edmonton, Alberta, Canada. Meets second Tuesday of each month, October to May.

Faculty of Radiologists
Honorary Secretary, Dr. J. N. Pattinson, 47 Lincoln's Inn Fields, London, W.C.2, England. Annual meeting: Cambridge, England, June 18–19, 1965.

Faculty of Radiologists, Royal College of Surgeons in Ireland
Registrar, Dr. H. O'Flanagan, F.R.C.P.I., D.P.H., 123 St. Stephens Green, Dublin 2, Ireland.

Section of Radiology of the Royal Society of Medicine (Confined to Medical Members)
Meets third Friday each month at 4:45 P.M. at the Royal Society of Medicine, 1 Wimpole St., London, W. 1, England.

Canadian Association of Radiologists
Honorary Secretary-Treasurer, Dr. D. J. Sieniewicz, *Associate Honorary Secretary-Treasurer*, Dr. Maurice Dufresne, 1555 Summerhill Ave., Montreal 25, Que., Canada. Annual meeting: Royal York Hotel, Toronto, Ontario, Feb., 24–28, 1965.

Montreal Radiological Study Club
Secretary, Dr. Leonard Rosenthall, Montreal General Hospital, Montreal, Que., Canada. Meets first Tuesday evening, October to April.

Section of Radiology, Canadian Medical Association
Secretary, Dr. C. M. Jones, Inglis St., Ext. Halifax, N. S.

Société Canadienne-Française d'Electro-Radiologie Médicale
General Secretary, Dr. Maurice Dufresne, 1560 Sherbrooke (East), Montreal, Que., Canada. Meets third Saturday each month.

Toronto Radiological Society
Secretary, Dr. Wallace M. Roy, St. Joseph's Hospitals, 30 The Queensway, Toronto 3, Ont., Canada. Meets second Monday of each month, September through May.

College of Radiologists of Australasia
Honorary Secretary, Dr. E. A. Booth, c/o British Medical Agency, 135 Macquarie St., Sydney, N.S.W., Australia.

South America

Asociación Argentina de Radiología
Secretary, Dr. Lidio G. Mosca, Avda. Gral. Paz 151, Córdoba, Argentina. Meetings held monthly.

Ateneo de Radiologia
Secretary, Dr. Victor A. Añaños, Instituto de Radiologia, Santa Fe 3100, Rosario, Argentina. Meets monthly on second and fourth Fridays at 7:00 p.m. in the Hospital Nacional de Centenario, Santa Fe 1300, Rosario.

Colégio Brasileiro de Radiologia
Secretary-General, Dr. Tede Eston de Eston, Caixa Postal 5984, São Paulo, Brazil.

Sociedad Argentina de Radiologia
Secretary, Dr. Armando B. de Onaindia, Santa Fe 1171, Buenos Aires. Meetings are held monthly.

Sociedad Bolivana de Radiología
Secretary, Dr. Javier Prada Méndez, Casilla 1596, La Paz, Bolivia. Meets monthly. General assembly once every two years.

Sociedade Brasileira de Radiologia
Secretary, Dr. Nicola Caminha, Av. Mem. de Sa, Rio de Janeiro, Brazil. General Assembly meets every two years in December.

Sociedade Brasileira de Radioterapia
Secretary, Dr. Oscar Rocha von Pfuhl, Av. Brigadeiro Luiz Antonio, 644, São Paulo, Brazil. Meets monthly on second Wednesday at 9:00 p.m. in São Paulo at Av. Brigadeiro Luiz Antonio, 644.

Sociedad Chilena de Radiología
Secretary, Dr. J. P. Velasco, Avenida Santa María 0410, Santiago, Chile. Meets fourth Friday of each month.

Sociedad Colombiana de Radiologia
Secretary, Dr. Armando Uribe, Hospital Miltar Central, Apartado aéreo No. 5804, Bogotá, Colombia. Meets last Thursday of each month.

Sociedad Ecuatoriana de Radiología y Fisioterapía
Secretary, Dr. Luis Blum, P.O. Box 3712, Guayaquil, [illegible]ador.

Sociedad Paraguaya de Radiología
Secretary, Dr. Miguel González Addone, 15 de Agosto 322, Asunción, Paraguay.

Sociedad Peruana de Radiologia
Secretary, Dr. Vicente Ubillus, Apartado 2306, Lima, Peru. Meets monthly except during January, February and March, at Asociación Médica Peruana "Daniel A. Carrión," Villalta 218, Lima.

Sociedad de Radiologica del Atlantico
Secretary, Dr. Raul Fernandez, Calle 40 #41–110, Baranquilla, Colombia. Society meets monthly at the Instituto de Radiologia.

Sociedad de Radiología, Cancerología y Física Médica del Uruguay
Secretary-General, Dr. Ernesto H. Cibils, Av. Agraciada 1464, piso 13, Montevideo, Uruguay.

Sociedade de Radiologia de Pernambuco
Secretary, Dr. Manoel Medeiros, Instituto de Radiologia da Faculdade de Medicina da Universidade do Recife, Caixa Postal 505, Pernambuco, Brazil.

Sociedad de Roentgenologia y Medicina Nuclear de la Provincia de Córdoba
Secretary-General Dr. Carlos A. Oulton, Santa Rosa 447, Córdoba, Argentina.

Sociedad Venezolana de Radiología
Secretary-General, Dr. Rubén Merenfeld, Apartado No. 9362 Candelaria, Caracas, Venezuela. Meets monthly third Friday at Colegio Médico del Distrito Federal, Caracas.

Continental Europe

Österreichische Röntgen-Gesellschaft
President, Dr. Konrad Weiss, Mariannengasse 10, Vienna 9, Austria. Meets second Tuesday of each month in Allgemeine Poliklinik. Annual meeting to be announced.

Société Belge de Radiologie
General Secretary, Prof. Simon Masy, Louvain, Belgium. Meets in February, March, May, June, September, October, November and December.

Société Européenne de Radiologie Pédiatrique
Permanent Secretary, Dr. Jaques Sauvegrain, Hôpital des Enfants-Malades, 149, rue de Sèvres, Paris 15e, France.
General Secretary, Dr. Ole Eklöf, P.O. Box, Stockholm 60, Sweden. Annual meeting: Stockholm, Sweden, May 20–22, 1965.

Société Française d'Electroradiologie Médicale, and its branches: Société du Sud-Ouest, du Littoral Méditerranéen, du Centre et du Lyonnais, du Nord, de l'Ouest, de l'Est, et d'Alger et d'Afrique du Nord. Central Society meets third Monday of each month, except during July, August and September, rue de Seine 12, Paris, France.
Secretary-General, Dr. Ch. Proux, 9 rue Daru, Paris 8^{e}, France.

Československá Společnost pro Roentgenologii a Radiologii
Secretary, Dr. Robert Poch, Praha 12, Srobárova 50, Czechoslovakia. Meets monthly except during July, August, and September. Annual general meeting.

Deutsche Röntgengesellschaft
Secretary, Professor Dr. med. H. Lossen, Universitäts-Röntgeninstitut., Lagenbeckstr. 1, Mainz, Germany.

Società Italiana di Radiologia Medica e di Medicina Nucleare
Secretary, Dr. Ettore Conte, Ospedale Mauriziano, Torino, Italy. Meets annually.

Nederlandse Vereniging voor Radiologie
Secretary, Dr. H. F. O. Stricker, Schalklaar, Netherlands.

Scandinavian Roentgen Societies
The Scandinavian roentgen societies have formed a joint association called the Northern Association for Medical Radiology, meeting every second year in the different countries belonging to the Association.

Sociedad Española de Radiología y Electrología Médicas y Medicina Nuclear
Secretary, Dr. D. Aureo Gutierrez Churruca, Esparteros, No. 9, Madrid, Spain. Meets monthly in Madrid.

Schweizerische Gesellschaft für Radiologie und Nuklearmedizin (Société Suisse de Radiologie et de Médecine Nucléaire)
Secretary, Dr. Max Hopf, Effingerstrasse 47, Bern, Switzerland.

Asia

Indian Radiological Association
Secretary, Dr. R. F. Sethna, Navsari Building, Hornby Road, Bombay 1, India.

Indonesian Radiological Society
Secretary, Professor Sjahriar Rasad Taman Tjut Mutiah 1, Diakarta, Indonesia.

ABSTRACTS OF RADIOLOGICAL LITERATURE

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ROENTGEN DIAGNOSIS

SKELETAL SYSTEM

MORTENS, J., and CHRISTENSEN, P. Traumatic separation of the upper femoral epiphysis as an obstetrical lesion. *Acta orthop. scandinav.*, 1964, *34*, 239–250. (From: Department III, the Orthopaedic Hospital, Copenhagen, Denmark.)

Two cases of traumatic upper femoral epiphyseal separation in the newborn are presented. Each was followed for approximately 4 years with very little resultant deformity. One received no treatment, and the other was placed in a Jones' splint for 6 weeks. Calcification in hematoma or callus confirmed the diagnosis in each instance, there being no bony fracture visible.

The authors could find no report in the literature of a traumatic hip dislocation proved to be an obstetrical lesion, but about 40 cases could be assessed as a traumatic obstetrical separation of the upper femoral epiphysis. The final outcome as to permanent deformity is unknown.

It is suggested that cases met with later in childhood of monolateral coxa vara with no gross structural alterations of the collum or around the epiphyseal subcapital plate might have peen of traumatic origin during birth.—*Arch H. Hall, M.D.*

NEUFELD, A. H., MORTON, H. S., and HALPENNY, G. W. Myelomatosis with xanthomatosis multiforme. *Canad. M. A. J.*, Aug. 22, 1964, *91*, 374–380. (From: Department of Pathological Chemistry, University of Western Ontario and Victoria Hospital, London, Ontario, and Departments of Medicine and Surgery, McGill University and Queen Mary Veterans Hospital, Montreal, Quebec.)

The authors present a case study of a 45 year old man who developed simultaneously xanthomatosis multiforme and myelomatosis. Initial studies when the xanthomatosis first appeared, showed very high levels of blood cholesterol, the major part of which was present in a markedly elevated beta-lipoprotein fraction.

Seven months after the onset of this disease roentgenographic examination of the lumbar spine showed generalized decalcification of the lumbar vertebrae. Bone marrow studies revealed the presence of large nucleated plasma cells which comprised 62 per cent of the nucleated cells. The clinical course of the disease over the remaining 5 years was marked by progressive collapse of vertebrae, spontaneous fractures of both femurs and the right humerus, as progressive osteoporosis occurred.

Special studies utilizing electrophoresis, ultracentrifugations, determinations of chemical composition, and incorporation with C^{14} labelled glutamic acid and acetate, indicated a direct relationship between the two conditions.

The authors postulate that the myeloma lipoprotein was apparently produced by the abnormal plasma cells in the bone marrow.

Six other cases have been reported possibly similar to this one, but not as completely investigated.—*James R. Knapp, M.D.*

PAPILLON, J., CROIZAT, P., REVOL, L., CHASSARD, J. L., BOTHIER, F., and COSTE, J. Les localisations osseuses de la lymphogranulomatose maligne. (The osseous localization of malignant lymphogranulomatosis.) *J. de radiol., d'électrol. et de méd. nucléaire*, Mar.–April, 1964, *45*, 109–116. (From: Chaire de Radiologie du Centre Léon-Bérard et de la Clinique médicale, Lyon, France.)

The authors report 53 cases of osseous involvement in Hodgkin's disease out of 370 patients—an incidence of 14.3 per cent.

Topographically, the bones with rich blood supply such as the dorsal and lumbar vertebrae, the ribs, the pelvis and the sternum, and to a lesser extent the femur, the clavicle, the skull and the scapula were involved. The lesions were usually multifocal, and had a tendency of appearing on the second and fourth years of the disease. The latter ones were of very poor prognosis.

The roentgen changes were mostly osteolytic in nature or in the form of an erosion when the invasion occurred from contiguous lymph nodes. Pure osteolysis was noted in the more central locations.

The osteolytic manifestations represented 57 per cent; 33 per cent were of the mixed type, consisting of osteolysis and osteosclerosis, and 10 per cent were of the pure osteosclerotic type.

A distinction between the primary and secondary involvement is made and the theory of lymphangitic invasion of the bone through the haversian canals is postulated.

The treatment of osseous involvement of Hodgkin's disease is both chemical and by roentgen or telecobalt irradiation, the immediate purpose being alleviation of pain.—*Jirair N. Sarian, M.D.*

NORDENTOFT, ERIK L. The accuracy of orthoroentgenographic measurements. *Acta orthop. scandinav.*, 1964, *34*, 283–288. (From: Orthopaedic Hospital, Copenhagen, Denmark.)

Orthoroentgenographic measurements on the lower extremities of 29 patients were made on each of two separate occasions and the results scientifically evaluated.

A 40×90 cm. cassette was used with the tube centered, respectively, over the hip, knee, and ankle joints. Variations of ± 2.86 mm. occurred when the whole extremities were measured, but the variations were much less when only one bone was examined. Movements of legs between single exposures and inaccuracy of positioning at separate examinations were the major sources of error.

The author concludes that this method is sufficiently exact for clinical use, but errors may influence scientific results.—*Arch H. Hall, M.D.*

BLOOD AND LYMPH SYSTEM

FONTAINE, R., WARTER, P., WEILL, F., TUCHMANN, L., and SUHLER, A. Les altérations morphologiques des os de la jambe déclenchées par les troubles circulatoires veineux des membres inférieurs. (Morphologic changes of the leg bones brought about by venous circulatory disorders in the lower extremities.) *J. de radiol., d'électrol. et de méd. nucléaire*, May, 1964, *45*, 219–224. (From: Clinique Chirurgicale A de Strasbourg, France.)

Osteoperiosteal changes frequently involve the bones of the leg following trophic disorders due to varicose veins, or as sequelae of venous thrombosis. These lesions have been known since Reclus (1884), but more attention has been devoted to the subject since 1945. More recently (1960), Lippmann and Goldin reported the frequent occurrence of subcutaneous calcification and ossification accompanying these bone alterations.

The periosteal appositions may appear like candle-drippings, or may be mammillated, lacy, spiculated, or lamellated. The diaphyseal cortex may become dense and thickened, masking the medullary cavity. It may also be thinned and porotic, mostly on the endosteal side, which results in a loss of differentiation between cortex and medulla.

These various structural changes are often intermingled. Even when extensive, the lesions remain localized to the tibia and fibula, always sparing the femur. They are identical, whether caused by essential varices or by a thrombosis.

Of 68 cases selected at random, 44.1 per cent showed bony alterations: 46 of these patients were suffering from postphlebitic ulcers and 22 had varicose ulcers with integrity of the deep veins, verified by phlebography. The etiology of the initial venous thrombosis does not influence the aspect of the bone lesions, and these become manifest up to 15 years later (minimum 3 years). Superficial venous thromboses were seen as frequently in those patients with bone changes as in those without them. The only constant finding was the development of superficial varices, symptomatic of a deep obliteration, in 47.6 per cent of the patients with bone lesions, as opposed to 4 per cent of those without bone lesions. In the few cases where an arteriography was performed, arteriovenous shunts were regularly seen. No relation exists between the extent of bone involvement and the size of cutaneous ulcers or their degree of infection.

The cause of these bone lesions associated with venopathies is still unknown. The authors believe that they are produced by a local effect. These lesions co-exist mostly with ulcers or retractile cutaneous sclerosis or thickened tegument fixed to the deep tissues. They are exceptional where the skin has remained perfectly smooth. They are seen on a background of venous stasis which exists with essential varices, or may result from a thrombosis. This venous stasis is accompanied by subcutaneous edema and regional hyperemia, with a consequent local calcium deposition. This hypothesis was previously advanced by Leriche and Policard.

The roentgenologic diagnosis is easy when the clinical data are known. When the alterations are diffuse, all forms of periostitis, syphilitic or osteomyelitic, should be considered. If the bone lesion is localized, the differential diagnosis should include cortical osteomyelitis and sometimes osteosarcoma.—*H. P. Lévesque, M.D.*

NGU, V. ANOMAH. The lymphatic drainage of the leg and its implications. *Clin. Radiol.*, July, 1964, *15*, 197–201. (From: Department of Surgery, Ibadan University, Nigeria.)

The different anatomic forms of acquired lymphedema seen in the lower limbs in Nigeria pose interesting problems. In some patients, the swelling stops at the knee, not spreading up the leg to involve the thigh. This may lie partly in the anatomic disposition of the lymphatic drainage at different levels in the leg and in part on the pathologic processes responsible for the lymphedema.

A lymphangiographic study of the separate lymphatic drainage of the thigh and lower leg was carried out on 20 healthy volunteer subjects. This was supplemented by an anatomic study on 5 cadavers. Only the main lymph trunks draining the subcutaneous tissues were studied. Deep lymphatics did not form part of this investigation.

After lymphangiography on cadavers, dissection of the inguinal region showed that the lymph nodes to which the thigh and lower leg vessels drained together form the vertical chain of superficial inguinal lymph nodes. Lower leg vessels drained into the lowest lymph nodes of the chain which lie at the apex of the femoral triangle and which on roentgenograms are opposite the lesser trochanter. Thigh vessels drained into lymph nodes near the upper end of the chain, close to the saphenous opening and on roentgenograms opposite to the head or the neck of the femur. In one of the living subjects a lymph vessel from the thigh passed directly to the posterior abdominal wall without apparent interruption at an inguinal lymph node.

A clinical study of patients with inflammatory lymphedema arising from the lower leg has shown that the lymphedema is localized below the knee and remains so. Lymphangiographic studies in such cases have demonstrated diseased vessels extending from the lower leg to the lowest lymph nodes of the vertical inguinal chain which were also affected. Vessels draining the thigh were, however, normal in all respects and drained to separate lymph nodes above the diseased group.

These findings are consistent with a separate and distinct lymph drainage for the lower leg and for the thigh. This protects the thigh from pathologic processes involving the lower leg. Occasional lymph vessels from the leg which bypass inguinal lymph nodes altogether drain directly into para-aortic lymph nodes. Malignant melanomas spreading by such vessels may give rise to para-aortic metastases at a stage when the inguinal lymph nodes are clinically free of disease.—*Samuel G. Henderson, M.D.*

NORIEGA L., JOSÉ, RÍOS SAN MARTÍN, GUSTAVO, and FALCÓ, JORGE. Intraosseous phlebography and lymphadenography in carcinoma of the cervix and other pelvic neoplasia. *Radiology*, Aug., 1964, *83*, 219–227. (Address: Tepic 126, Mexico City, Mexico.)

Combined phlebography and lymphadenography were done in a study of 52 patients: to attempt the diagnosis of metastatic carcinoma not detectable by ordinary means; to evaluate treatment of malignant disease; and to obtain a better knowledge of the venous and lymph node pathology associated with pelvic neoplasia. The intraosseous venography was performed by injecting the femoral trochanters bilaterally with Vasurix, with the patient under general anesthesia. Roentgenography was carried out with a Schönander serial changer. The most common evidence of neoplasia in this series consisted of: (1) a sudden halt in the flow of the contrast medium due to obstruction; (2) narrowing of a vessel; (3) absence of filling of a major vessel; (4) presence of collateral circulation; and (5) marked stasis.

Lymphadenography was done after the method of Kinmonth, and signs of neoplasia most frequently observed were: (1) displacement of lymph vessels; (2) reflex to visceral systems; (3) persistent filling of the vessels; (4) enlarged lymph nodes; and (5) crescentic or peripheral ring filling defects in lymph nodes.

The method was most useful for the detection of deep recurrences following surgery or radiation therapy, and not as useful in early stages. In 7 of the 52 cases venous alteration around a suspicious lymph node area confirmed a suspicion of tumor. The authors feel that the method should be employed more frequently.—*James C. Moore, M.D.*

GENERAL

GERSHON-COHEN, J., and FORMAN, MYRON. Mammography of cancer. *Bull. New York Acad. Med.*, Sept., 1964, *40*, 674–689. (From: Department of Radiology, Albert Einstein Medical Center, Northern Division, Philadelphia, Pa.)

Initial work in mammography is credited to Salomon in Germany some 50 years ago. A short summary is made of the significant contributions to this field from the initial work to the present time. The authors feel that satisfactory results are obtained using nonscreen films rather than industrial film, but suggest that the roentgenologist use the technique which to him is most satisfactory.

Although 90 per cent of breast cancer is initially discovered by the patient, the authors believe that the patient may often deny a long period of self observation of a breast mass. A correct preoperative diagnosis in a series of 500 consecutive breast cancers was obtained in only 48 per cent of the cases examined by the surgeon and 90 per cent of the cases by roentgenologic examination. It is, therefore, suggested that routine use of mammography should result in securing more prompt biopsies of smaller lesions, less frequently associated with regional metastasis.

By a combination of clinical and roentgenographic studies, it should be possible to detect more than 95 per cent of all malignant lesions of the breast.

The authors present a classification of mammary cancers based on the roentgenographic appearance.—*James R. Knapp, M.D.*

FUNDERBURK, WILLIAM W., SYPHAX, BURKE, and SMITH, C. W. Contrast mammography in breast discharge. *Surg., Gynec. & Obst.*, Aug., 1964, *119*, 276–280. (From: Tumor Clinic and Department of Surgery and Radiology, Howard University and Freedmen's Hospital, Washington, D. C.)

Breast discharge should be considered abnormal in the nonlactating breast unless proof is established to the contrary. Injection of contrast media into lactiferous ducts has long been known as an accurate method of studying these breasts. Opaque media used in the past, however, resulted in a high incidence of abscess, nonsuppurative mastitis and foreign body reaction.

The authors report in detail a method to inject affected ducts. Fifty per cent diatrizoate sodium was used in 90 per cent of the cases (the medium used in the remaining cases was not mentioned). Forty patients received 86 injections.

Follow-up failed to reveal any complications.—*George A. Miller, M.D.*

RADIATION THERAPY

VOORHESS, MARY L., and WHALEN, JOSEPH P. Role of catecholamine excretion in diagnosis and treatment of neuroblastoma: report of two cases. *Radiology*, July, 1964, *83*, 92–97. (From: Departments of Pediatrics and Radiology, State University of New York, Upstate Medical Center, Syracuse, N. Y.)

Recent investigations in several laboratories have demonstrated abnormal urinary excretion of the catecholamines, their precursors and metabolites in patients with neuroblastoma, ganglioneuroblastoma, and ganglioneuroma. Because of this the radiologist now has a very specific laboratory test to aid in the differential diagnosis of an abdominal mass in infants and children. Serial measurements of these compounds have also proved most helpful in determining the effectiveness of irradiation and chemotherapy.

The purpose of this paper is to illustrate by 2 case reports the importance of these catecholamine measurements in the handling of 2 patients with neuroblastoma.

Case I was a 9 week old boy with a right upper quadrant mass. At laparotomy an inoperable tumor was found which was separate from the right kidney but had metastasized to the liver. Surgical biopsy and histologic study revealed the presence of neuroblastoma. The abnormally high urinary excretion of catecholamines initially present decreased after the first course of irradiation and chemotherapy but did not reach normal levels. Because of this another laparotomy was performed and residual unresectable tumor, proven by biopsy, was found. Following subsequent radiation therapy of this residual tumor the catecholamine excretion returned to normal and has remained there for the past 15 months.

Case II was a 3 year old girl in whom a diagnosis was made following the discovery of a left upper quadrant mass. Her abnormally high catecholamine excretion, present initially, also decreased following irradiation and chemotherapy but never reached normal levels. When these levels began to increase a second abdominal exploration revealed residual unresectable tumor plus another large mass in the cul de sac. Subsequent irradiation gave some palliation but a continued rise in the catecholamine excretion showed lack of control of the malignancy which eventually caused the death of the patient.

The authors comment also on the chronic diarrhea which was present in the first patient (Case I). Chronic diarrhea, unresponsive to medical therapy, may occur in association with tumors of neural crest origin; following surgical removal of the tumor or successful chemotherapy and radiation therapy the diarrhea ceases.

The authors feel that an abnormaly high urinary catecholamine excretion in a patient with a chronic unresponsive diarrhea may provide the first clue to the pediatrician and radiologist that a tumor is present.—*Donald N. Dysart, M.D.*

BERMAN, HARRY L. The treatment of benign giant-cell tumors of the vertebrae by irradiation. *Radiology*, Aug., 1964, *83*, 202–207. (Address: Division of Radiation Therapy and Isotopes, Sinai Hospital of Baltimore, Inc., Baltimore 15, Md.)

Approximately 7 per cent of all benign giant-cell tumors occur within vertebrae, including the sacrum. Irradiation of these lesions is indicated because they are radioresponsive and their location contraindicates preferred surgical treatment.

There appears to be a direct correlation of delayed diagnosis and delayed treatment with complications of the disease process. Early laminectomy and immobilization, particularly of the cervical spine, prejudices a favorable result. These tumors, by virtue of bone destruction in a confined area, may result in compression and transection of the spinal cord.

Just as elsewhere, benign giant-cell tumors of vertebrae are aggressive in behavior with tendency toward recurrence and malignant degeneration. The occurrence of postirradiation sarcomatous changes is not clearly established. Being potentially radiocurable, therefore, these tumors could be treated with 4,500–5,000 r in 4 to 5 weeks.

Five case studies of proven giant-cell tumors of vertebrae are presented to illustrate their natural course and the effects of radiation therapy.—*John Bond, M.D.*

LEE, E. STANLEY. Surgery of irradiated tissues. *Proc. Roy. Soc. Med.*, July, 1964, *57*, 563–564. (From: Westminster Hospital, London, England.)

Surgery may be required as part of the total treatment plan because of failure to cure by irradiation or to repair radiation damage.

Recurrent skin cancers can usually be excised. In soft tissue tumors, wide excision can be performed about 6 weeks after therapy with skin sparing supervoltage irradiation. For breast cancer, surgery can be done after subsidence of the radiation reaction following a full course of radiation therapy. Head and neck neoplasms present serious problems. Pedicle flaps of unirradiated skin are often useful. In the pelvis, anastomosis of irradiated bowel or ureters is hazardous and colostomy or implantation of the ureters into an ileal conduit is preferred.

Ablative surgery can be done on heavily irradiated tissues with special attention to preoperative preparation, asepsis and hemostasis. Reconstructive surgery should employ tissue brought in from outside the treated areas. Large or rapidly growing lesions usually have a poor prognosis.—*Steven H. Cornell, M.D.*

NEWTON, KENNETH A. Some effects of irradiation to the bowel. *Proc. Roy Soc. Med.*, July, 1964, *57*, 565–569. (From: Westminster Hospital, London, England.)

Supervoltage apparatus enables the radiologist to deliver high doses to the abdominal cavity. This may result in serious intestinal complications.

Two cases are discussed in detail.

One patient with carcinoma of the cervix was given a tumor dose of 6,000 r in 53 days. One year after therapy, there was edema and fibrosis of the subcutaneous tissues. Two years after therapy, the patient complained of severe diarrhea; examination showed considerable narrowing and fibrosis of the rectum and vagina. Eleven years after therapy, the patient still leaks urine at night.

Extensive ulcerations of the stomach and large bowel were present at postmortem examination of a 6 year old child whose entire abdomen received a tissue dose of 1,120 r in 10 days. The treatment had been given for exacerbation of acute lymphatic leukemia.

For prophylactic irradiation of testicular teratoma, opposing fields are still used, but the field width is restricted to 10 cm. and the dose to 5,000 r in 5 weeks. Of 68 cases 2 had significant intestinal complications.

For disseminated abdominal malignancy, the use of intraperitoneal yttrium 90 has been abandoned. One patient's intestines were obstructed 2 weeks after therapy due to a fibrinous exudate.

In cobalt 60 therapy of carcinoma of the cervix using 2 centers of rotation, no persistent or late intestinal complications occurred when the dose at the 80 per cent isodose curve was under 5,000 r. Between 5,000 and 5,500 r, there was an 18 per cent complication rate; between 5,500 r and 6,000 r, 23 per cent; over 6,000 r, 41 per cent.

The author now restricts the dose at the 80 per cent isodose curve to 5,400 r and 2 weeks after external therapy inserts a 50 mg. radium tube into the uterine cavity for 36 hours. This technique has substantially lowered the rate of complications.—*Steven H. Cornell, M.D.*

RADIOISOTOPES

Mealey, John, Jr., Dehner, John R., and Reese, Isaac C. Clinical comparison of two agents used in brain scanning. *J.A.M.A.*, July 27, 1964, *189*, 260–264. (Address: Dr. Mealey, 1100 W. Michigan Street, Indianapolis, Ind.)

Chlormerodin Hg^{203} and radioiodinated serum albumin were used in each of 63 patients. The scans were read as unknowns and compared for accuracy and quality with the clinical information.

Doses of 10 μc/kg. body weight of chlormerodin Hg^{203} were used and scanning performed in 4–6 hours, employing an analyzer and scintillation scanner; with radioiodinated serum albumin, doses of 5.5 μc/kg. were used and scans were performed at 24 and 48 hours. Anteroposterior and lateral scans were obtained in each case by both print-out recordings and photoscans with a 3×2 inch sodium iodide crystal and a 19-hole focusing collimator.

Both isotope labeled compounds correctly localized 7 glioblastomas, 5 metastatic tumors, 3 meningiomas, 1 craniopharyngioma, 1 oligodendroglioma, and 1 cystic cerebral astrocytoma (Grade II), representing 78 per cent of the tumors. Neither agent detected 3 Grade I solid cerebral astrocytomas, 1 third ventricle tumor, and 1 large calcified plexus papilloma. Equivocal results were obtained by both agents in 1 astrocytoma.

Neither agent showed a clear-cut superiority, even in retrospect.

A unilateral subdural empyema and a chronic brain abscess were satisfactorily detected on all scans.

Of 7 patients with traumatic intracranial hematoma, radioiodinated serum albumin detected all at 24 hours, but only 5 at 48 hours. Chlormerodin Hg^{203} gave positive scans in only 5 patients. In retrospect, all scans could be read as positive from the anteroposterior views alone.

In 31 patients there were no focal lesions of surgical significance. Out of a total of 88 scans, there were no false positives or equivocal readings with chlormerodin Hg^{203} or false positives with radioiodinated serum albumin.

The authors conclude that some advantages from chlormerodin Hg^{203} used as a single study might be expected as compared to the 24-hour radioiodinated serum albumin scan. They feel that clinical considerations and temporal convenience indicate that the average patient should be scanned with chlormerodin Hg^{203} and that radioiodinated serum albumin should be used in equivocal cases or in children because of the lower renal dose.—*Richard R. Oslund, M.D.*

Cabassa, N., and Sciascia, R. Modificazioni del test di Hamolsky nel ratto dopo somministrazione di sostanze anticoagulanti (eparina e 4-ossicumarina). (Modifications of the test of Hamolsky in the rat after the administration of anticoagulant substances [heparin and 4-hydroxycoumarin].) *Radiobiol., radioter. e fisica medica*, Jan.-Feb., 1964, *19*, 3–9. (From: Istituto di Radiologia dell'Università di Bologna, Italy.)

The erythrocyte uptake of I^{131} triiodothyronine is a test of thyroid function which offers the following advantages: (a) easy execution; (b) the test is made on a blood sample which might have been taken 1 to 3 days before; and (c) it is not influenced by the administration of iodine.

The test is, however, influenced by several pathologic states, such as thyroiditis, hypoalbuminemia, respiratory insufficiency with acidosis, polycythemia and hyperthyroidism. In these cases the uptake is increased. In pregnancy, following the administration of estrogens, in hyperalbuminemia there is instead a diminished uptake of the labeled hormone.

The authors investigated whether the administration *in vivo* of heparin and 4-hydroxycoumarin would influence the test of Hamolsky.

Sixty male Sprague Dawley rats were used; fifteen were kept as controls. In 30, heparin was injected intravenously in an amount of 10 mg./kg. body weight, and in 25 rats the 4-hydroxycoumarin was given per os in decreasing daily doses, for 4 consecutive days, in an amount of 100 gamma per 100 gm. of weight.

An analysis of the results showed an increased erythrocyte uptake of I^{131} triiodothyronine in the rats treated with heparin, while in the rats treated with 4-hydroxycoumarin the test was not influenced by the drug.

It is believed that the mechanism of the increased erythrocyte uptake could be explained by an effect on the thyroid itself, or on the plasma, or on the erythrocytes. The authors favor the second hypothesis.—*A. F. Govoni, M.D.*

Anger, Hal O. Scintillation camera with multichannel collimators. *J. Nuclear Med.*, July, 1964, *5*, 515–531. (From: Donner Laboratory of Medical Physics and Biophysics and Lawrence Radiation Laboratory, University of California, Berkeley, Calif.)

The scintillation camera is an instrument which employs as its basic detector a single sodium iodide crystal 11½ inches in diameter by ½ inch thick. A close-packed hexagonal array of 19 photomultiplier tubes is coupled to the crystal through an optical light guide. The phototubes view overlapping areas in the scintillator so that light from each scintillation divides among the 19 tubes. The phototubes are connected to an analog computer which identifies the X and Y coordinates and the brightness of each scintillation occurring in the crystal. The image of these scintillations is produced upon an oscilloscope in the same relative positions in which they occurred in the scintillator. The flashes occurring on the oscilloscope screen are photographed over a period of time and an image of the subject results.

Three methods of collimation have been used with this now well-known device. Coincidence counting for positron emitters has been explored in the past, as has the use of this particular detector with a pinhole collimator. The latter device is at its most effective when the detector is viewing small objects, such as the thyroid gland. For larger fields of operation, for example the lungs, brain or liver, a collimator system which represents a large number of parallel holes gives the best sensitivity and resolution. Parallel channel collimators have a more uniform depth response than do focusing collimators and have a superior "depth of focus." Multichannel collimators are at their best with low-energy gamma rays, for the thin walls of the multiple tubes act as more efficient barriers. The principles of multichannel collimators are derived mathematically, and some applications are discussed. It is pointed out that a multichannel collimator can be designed to have the same resolution at a given depth as a focused collimator, but that throughout the range of depth in question all objects, whether in the "plane of focus" or not, will be more sharply resolved.

The principles of construction of multichannel collimators are reviewed in detail, and the article should be read in its entirety by anyone who contemplates working with low-energy emitters, or with an instrument of the family of the scintillation camera. Scans of various test objects are portrayed, and it is concluded that the sensitivity of the scintillation camera when used with multichannel collimators is appreciably higher than that of the focused collimator mechanical scanner. The saving in time of the scintillation camera is a very distinct advantage as well.—*Frederick J. Bonte, M.D.*

Cabassa, N., and Sciascia, R. Modificazioni della captazione eritrocitaria della T_3-I^{131} nel ratto dopo somministrazione di coagulanti (solfato di protamina e vit. K_1). (Modifications of the erythrocyte uptake of T_3-I^{131} in the rat after administration of coagulants [protamine sulphate and vitamin K_1].) *Radiobiol., radioter. e fisica medica*, Jan.-Feb., 1964, *19*, 24–28. (From: Istituto di Radiologia dell'Università di Bologna, Italy.)

The authors have investigated with experiments *in vivo* whether the administration of coagulants would influence the Hamolsky test of thyroid function.

Sixty male Sprague Dawley rats were used. Thirty were treated with protamine sulphate, 25 with vitamin K_1 and 15 were kept as controls.

The results obtained showed an increase in the erythrocyte uptake of I^{131} triiodothyronine in the rats treated with both drugs.

It is pointed out that the therapeutic administration of protamine sulphate and vitamin K_1 could, therefore, alter the test of Hamolsky.—*A. F. Govoni, M.D.*

Kawin, Bergene, Huston, Frank V., and Cope, Clyde B. Digital processing display system for radioisotope scanning. *J. Nuclear Med.*, July, 1964, *5*, 500–514. (From: Radioisotope Service and Testing and Development Center, Veterans Administration Hospital, Fort Howard, Md.)

A system is described wherein scintillation scan data are collected in the usual manner and transmitted automatically to a computer for processing and extraction of the best possible values. The computer thus may be located at some distance from the detection unit, and it may serve a number of detection units. In this particular system, scan data are rendered in the form of "iso-count contours" or profile maps of counting rate activity.

The workings of the system are described in great detail, and are illustrated by accompanying block diagrams.—*Frederick J. Bonte, M.D.*

Pochin, E. Eric. Radiation exposure from the use of radioiodine in thyroid disease. *Proc. Roy. Soc. Med.*, July, 1964, *57*, 564–565. (From: MRC Department of Clinical Research, University College Hospital Medical School, London, England.)

The use of radioactive iodine in thyroid disease contributes 0.6 per cent of the total exposure from medical radiation to the population as a whole.

The usual 5 μc test dose of I^{131} generally does not result in a dose greater than 10 rads in the individual patient. However, in the glands of fetuses, infants and children, 5 to 10 times higher exposures may result. In these cases, 5 μc of I^{132} will reduce the thyroid exposure to below 1 rad.

In the radioiodine therapy of hyperthyroidism, no evidence of an increased incidence of leukemia has been observed, nor has there been development of thyroid cancer.

In the radioiodine therapy of thyroid cancer, there is significant induction of leukemia, with a reported incidence of 2.3 per cent. However, this is a small risk when balanced against the likelihood of controlling disseminated malignancy.—*Steven H. Cornell, M.D.*

CHEMOTHERAPY

Study Committee of the Midwest Cooperative Chemotherapy Group. Multiple myeloma: general aspects of diagnosis, course, and survival. *J.A.M.A.*, May 25, 1964, *188*, 741–745. (Address: Dr. William R. Best, 1853 W. Polk Street, Chicago, Ill.)

This study of 185 patients with multiple myeloma was undertaken to provide possible criteria which might be used to evaluate therapy of the disease. Twenty-two Midwest institutions participated.

The most frequent findings leading to a clinical suspicion of multiple myeloma were bone pain and anemia. The diagnosis was most often established by demonstrating bone marrow abnormality.

The most distressing symptom to the patient was bone pain and it was also the commonest reason for beginning therapy. Administration of urethane alone or with other modalities was the usual treatment.

Survival after diagnosis was 90 per cent, 1½ months; 50 per cent, 8½ months; and 10 per cent, 56 months. Survival after the first symptom was estimated as 90 per cent, 5½ months; 50 per cent, 17½ months; and 10 per cent, 58 months.—*Henry J. Klos, M.D.*

Bloom, H. J. G., and Wallace, D. M. Hormones and the kidney: possible therapeutic role of testosterone in a patient with regression of metastases from renal adenocarcinoma. *Brit. M. J.*, Aug. 22, 1964, *2*, 476–480. (Address: Dr. Bloom, Consultant Radiotherapist, Royal Marsden Hospital, London, England.)

The relationship between the kidney and the endocrine system is perhaps greater than is generally appreciated. In experimental animals hypophysectomy results in a decrease in kidney weight, prevents compensatory hypertrophy, and reduces renal function. Administration of anterior pituitary extract causes renal hypertrophy.

Parathormone has a direct action on the normal kidney, increasing phosphate excretion probably by reducing tubular reabsorption. The kidney appears to fulfill the role of an endocrine gland by producing angiotensin, erythropoietin, and an "aldo-sterone-stimulating hormone" which may be renin.

In view of many endocrine factors influencing normal renal structure and function, the possibility of a hormonal background to renal adenocarcinoma in man was considered. This concept led to a trial of gonadal and corticosteroid hormones in patients with advanced cancer of the kidney. Between May 1959 and December 1963, 20 such patients were treated in this way at the Royal Marsden Hospital in London and followed to the time of death. Marked signs of tumor regression occurred in 4 cases.

Androgens were found to cause hypertrophy of the convoluted tubules and the parietal cells of Bowman's capsule in both intact and castrated mice of both sexes. Renal function in dogs and the degree of normal tubular hypertrophy in the remaining kidney, following unilateral nephrectomy in rats are increased by testosterone.

In male mice, castration brings about a fall in kidney size and testosterone an increase.

A number of clinical and pathologic observations support the idea of a hormonal background to the development and progress of renal carcinoma in man.

A case report is presented in detail of a male aged 58. Roentgen examination revealed metastases to the skull, tibia and left hilus from a renal adenocarcinoma. Injections of testosterone propionate were begun, 100 mg. intramuscularly daily, 5 days a week. Four weeks later his general condition had improved greatly. Eighteen months after starting testosterone, the patient gained some 50 lb.; the metastases in the skull and in the middle and lower end of the tibia (not irradiated) had disappeared; the right lung was clear and the left hilar mass was no longer evident. The patient enjoyed excellent health with no clinical or roentgenologic evidence of active disease for 35 months from the time testosterone therapy was started. Then, he developed generalization of the disease and expired. Necropsy revealed widespread metastases from renal adenocarcinoma in both lungs, the myocardium, thyroid, right adrenal, and the mediastinal and supraclavicular lymph nodes.

This patient is 1 of the 4 cases showing marked roentgenologic signs of regression in a series of 20 consecutive cases of progressive metastatic renal adenocarcinoma treated with various hormones. Regression in the 3 other cases was noted during treatment with Provera (6a-methyl-17a-hydroxyprogesterone acetate), a powerful synthetic progestational agent, practically devoid of androgenic and estrogenic properties. In these 3 patients the objective improvement was confined to pulmonary metastases and limited to periods of 3, 9, and 20 months. All 20 patients had multiple metastases and in 15 of them more than one organ was involved. Eight cases were considered "terminal" when hormone therapy was started.

The choice of endocrine treatment for a particular case of disseminated renal cancer must remain largely empirical.

Partial or complete natural regression of metastases in renal cancer is a well-recognized but rare phenomenon. Spontaneous disappearance of renal cancer appears nearly always to involve pulmonary metastases.

Hormone administration is not advocated at present for patients with limited or apparently quiescent metastatic disease. If the primary tumor is present and operable, a nephrectomy is performed and the metastases are observed for signs of spontaneous regression. Only when metastases are clearly advancing is hormone treatment introduced.—*Stephen N. Tager, M.D.*

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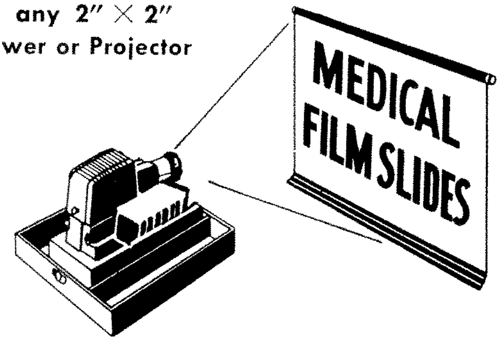

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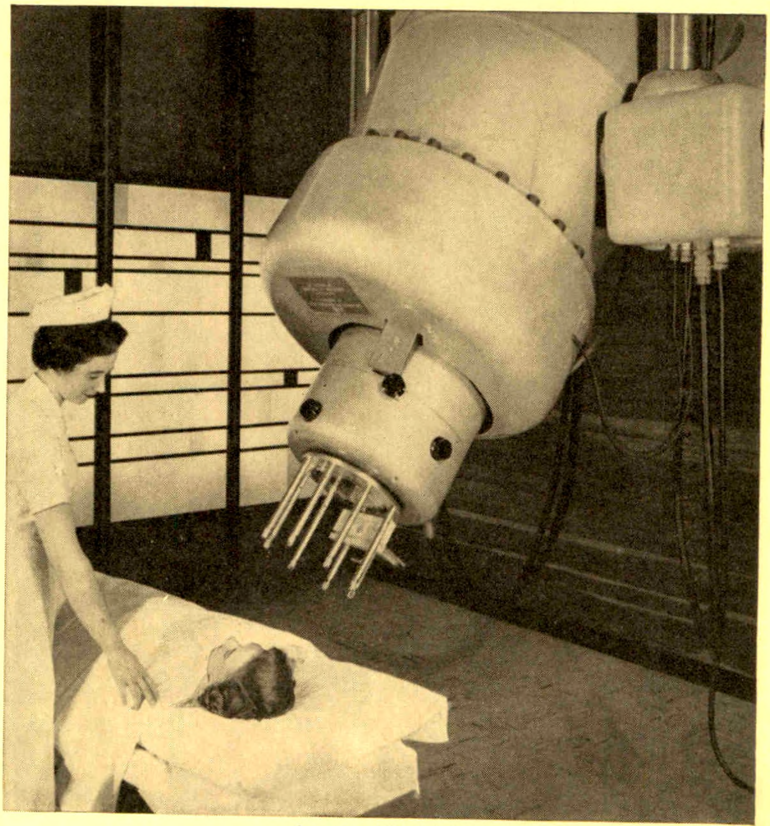

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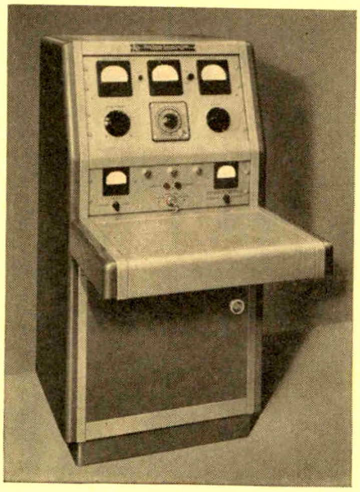

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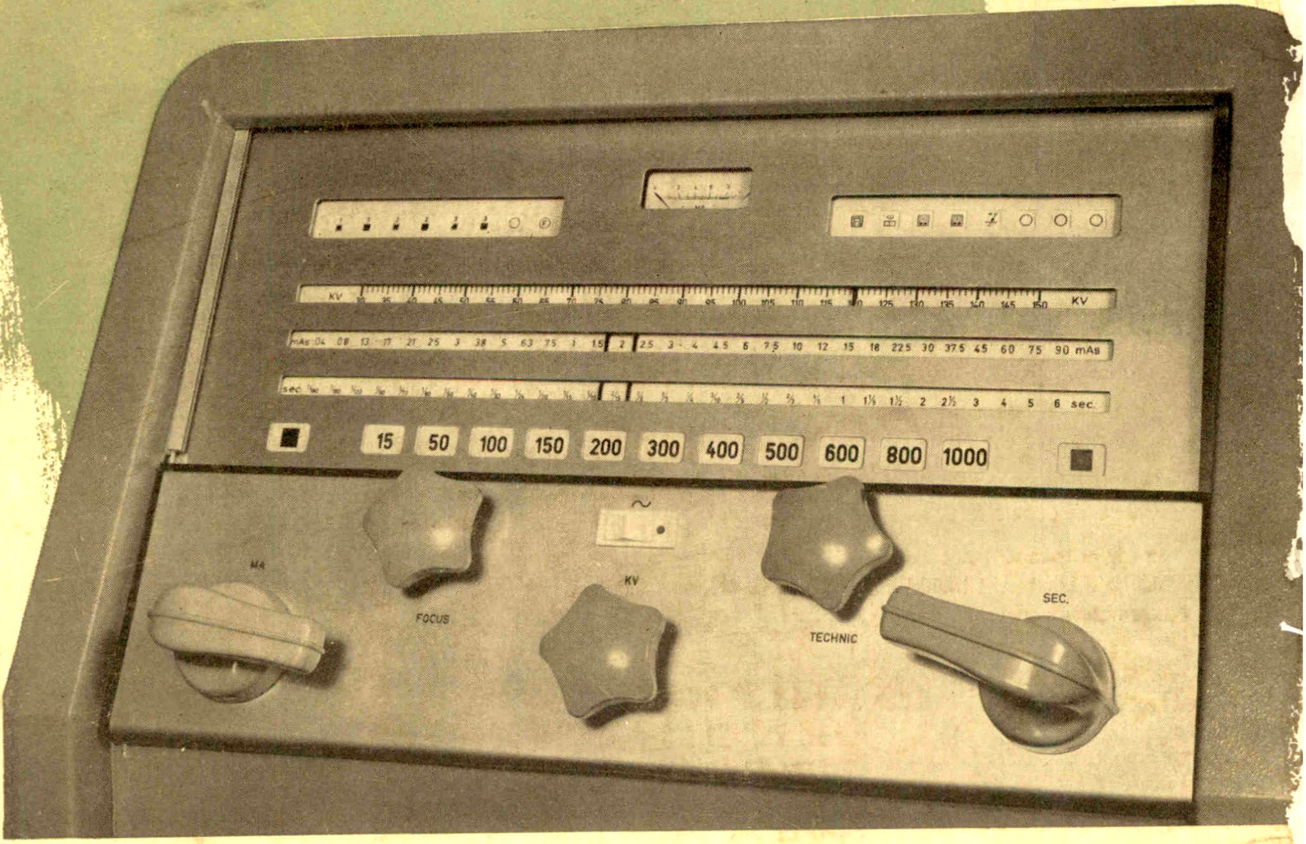

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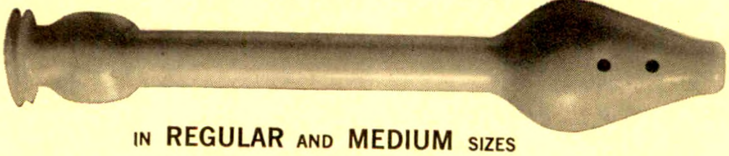

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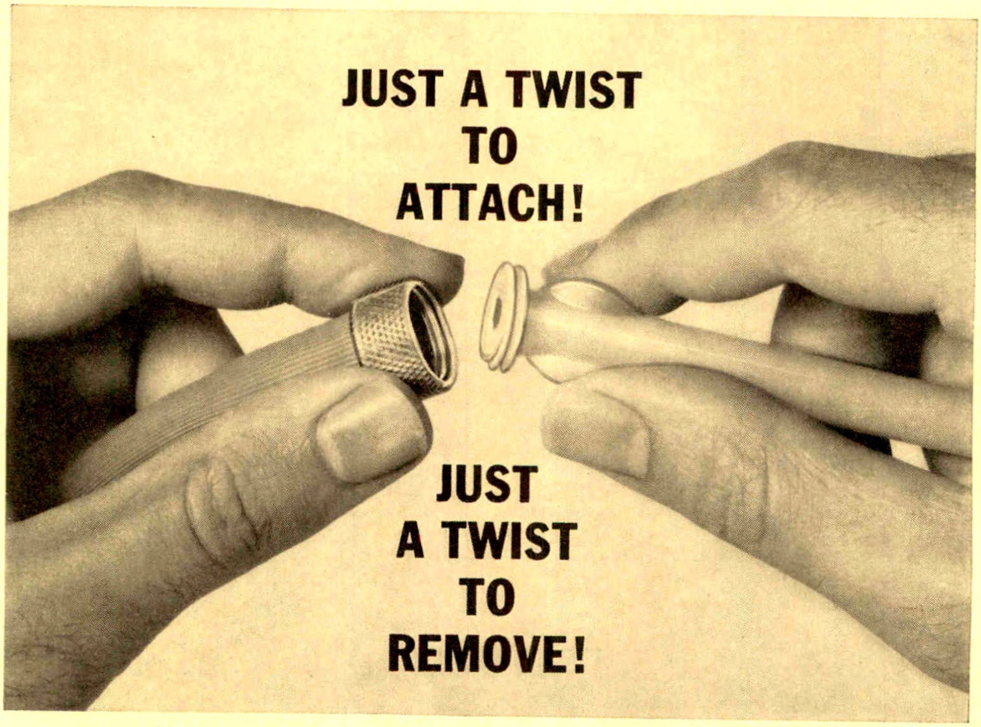

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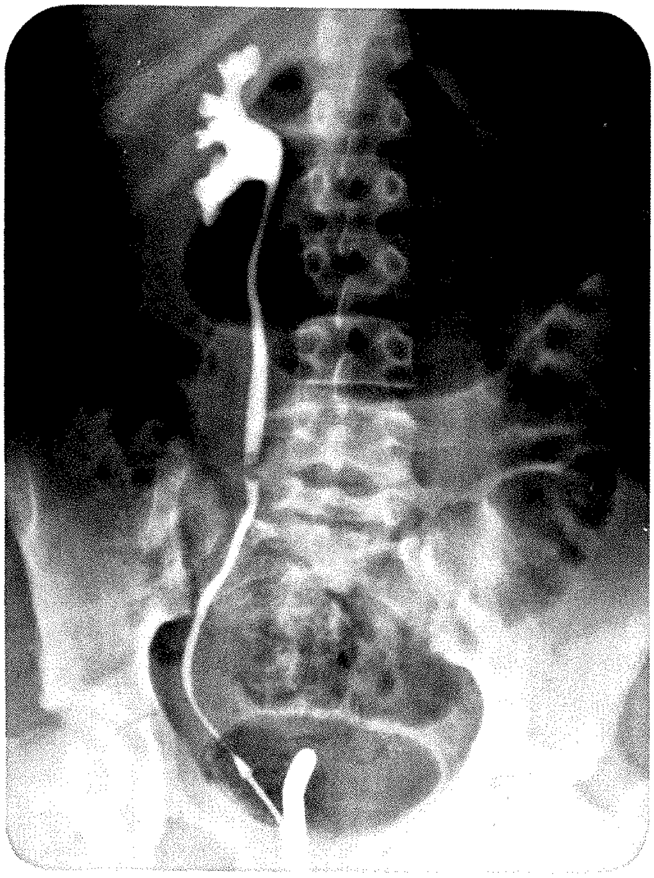

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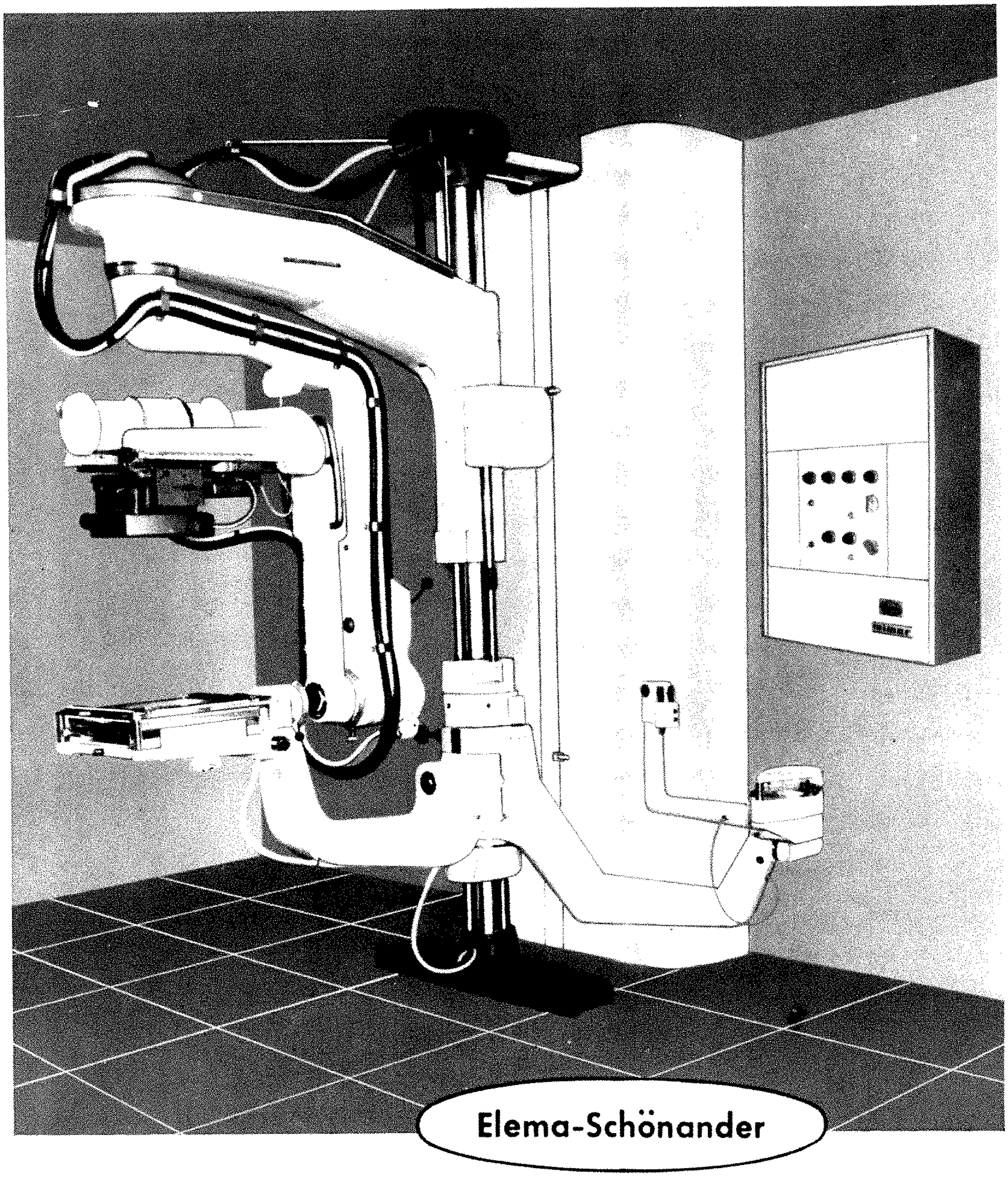

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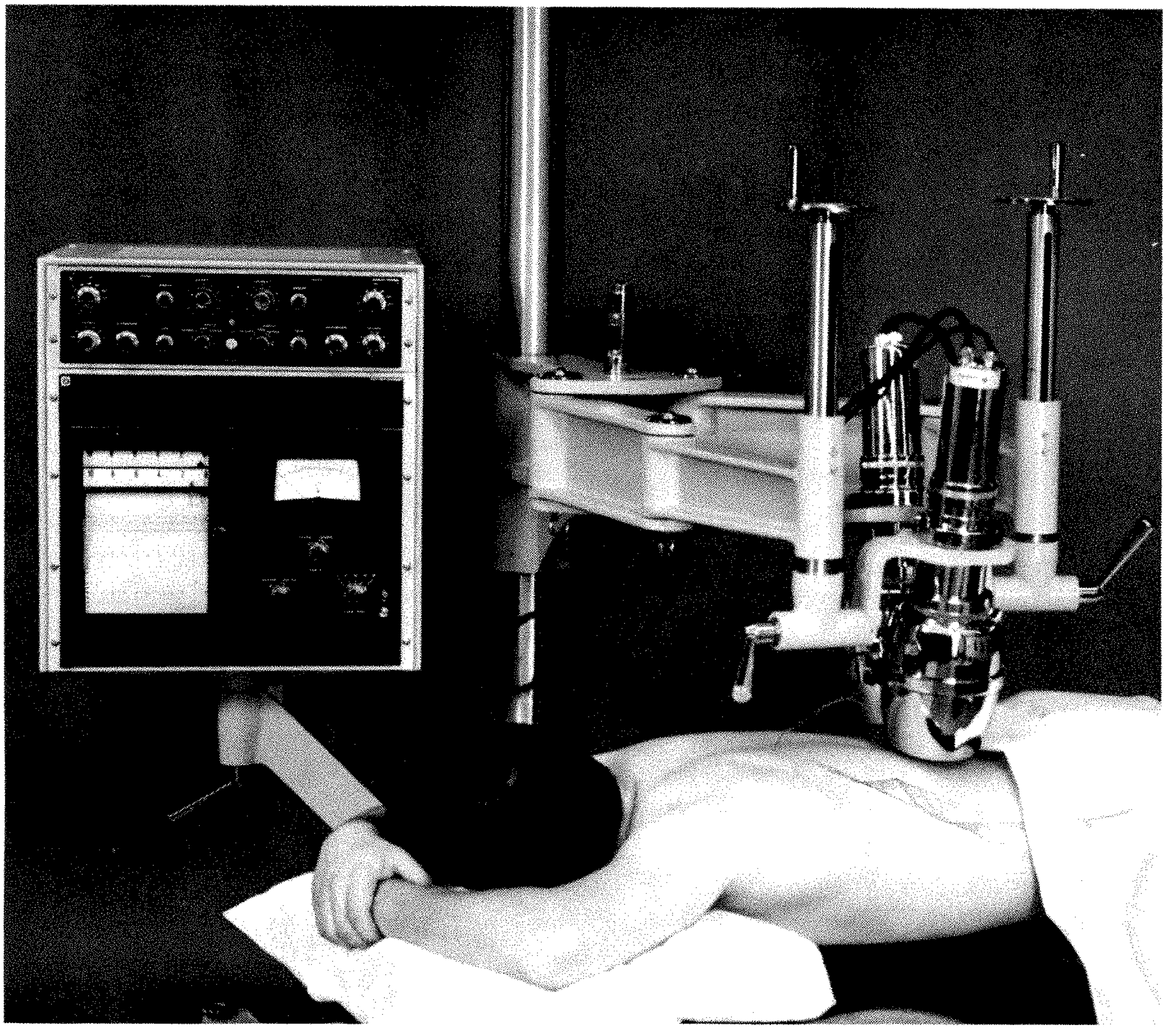

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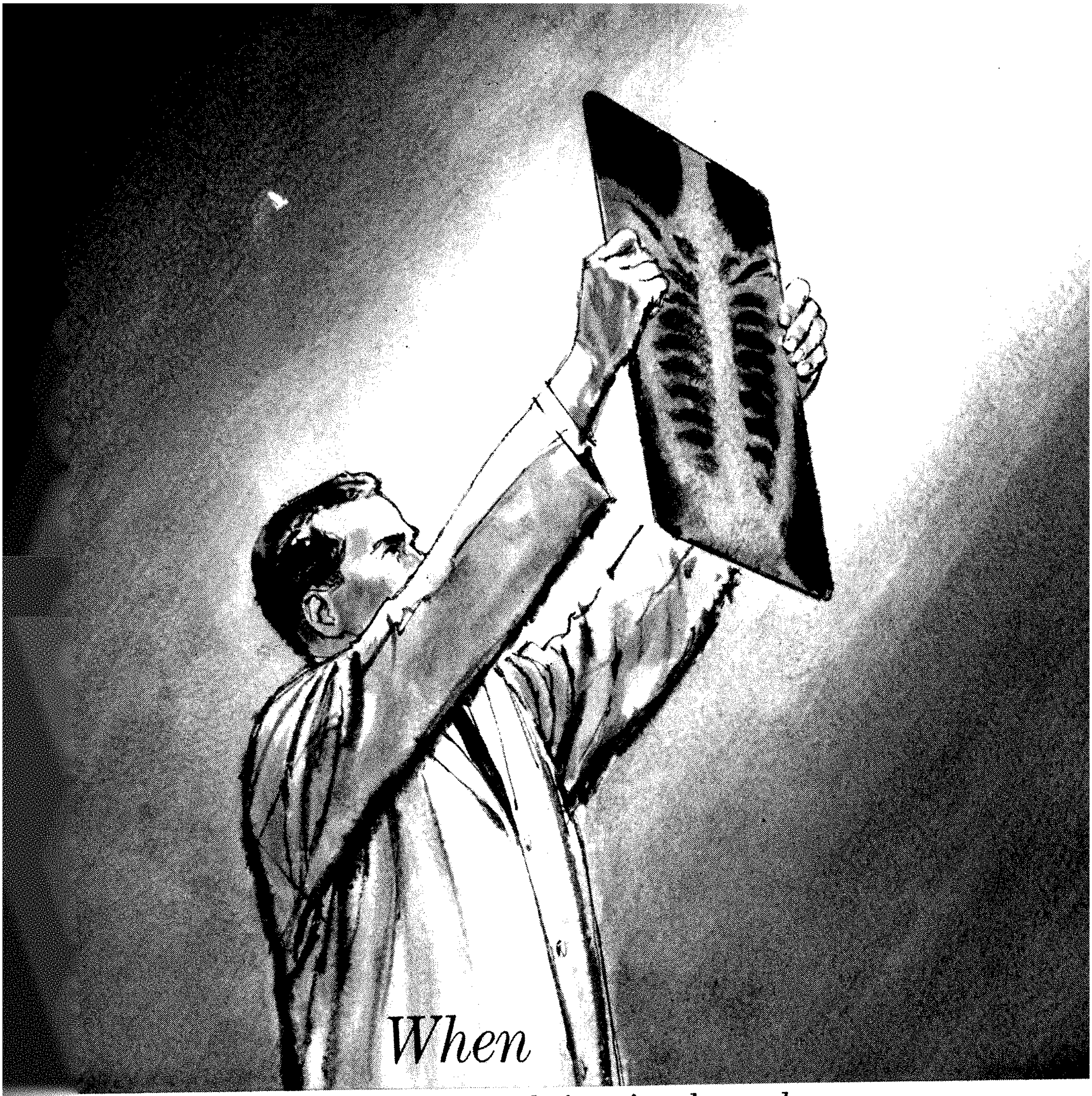

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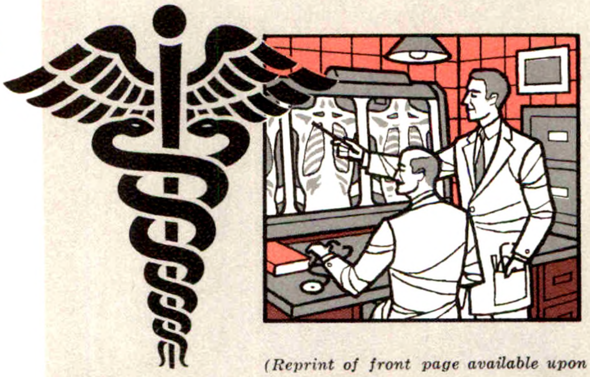
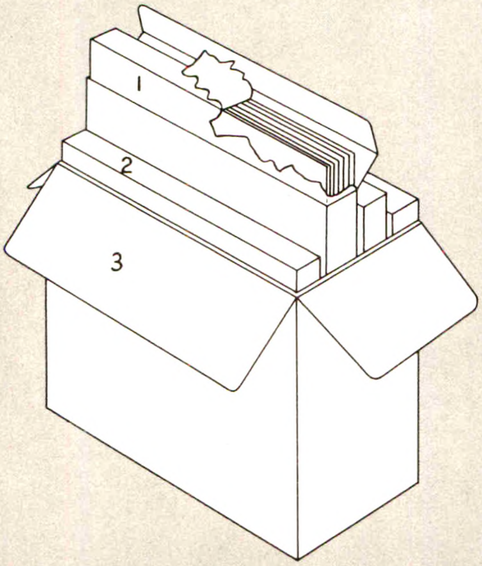


(Reprint of front page available upon request.)



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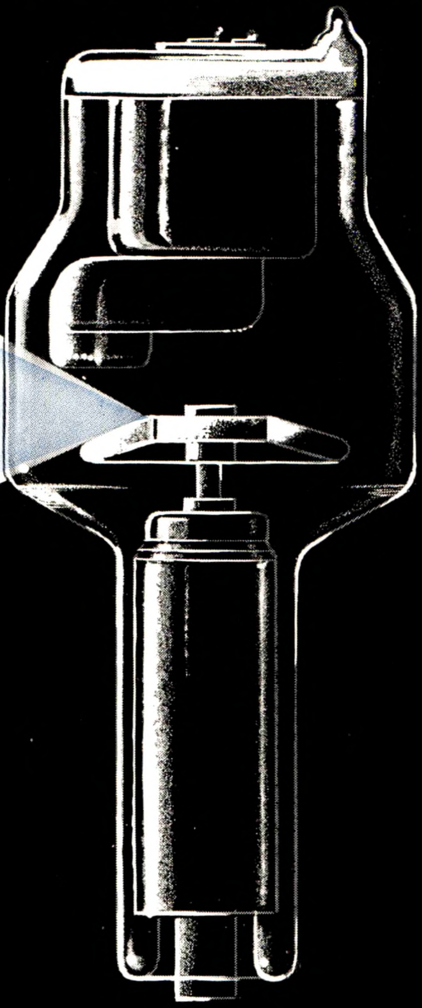

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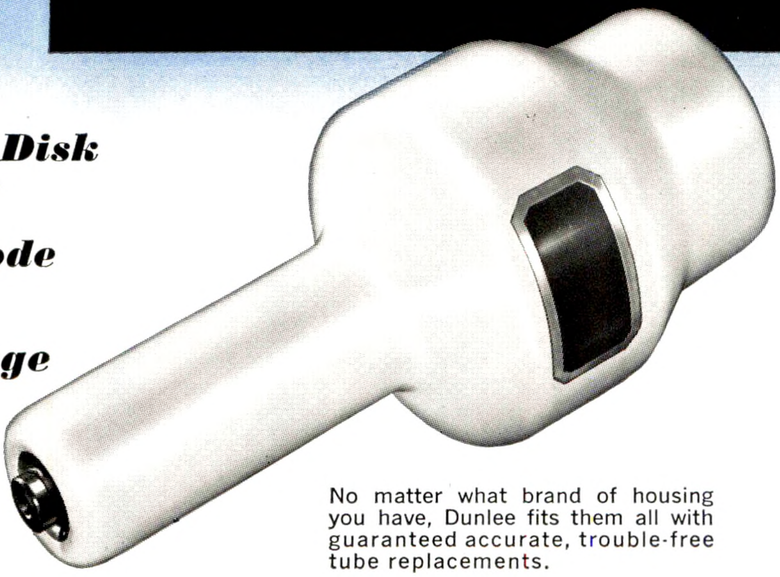

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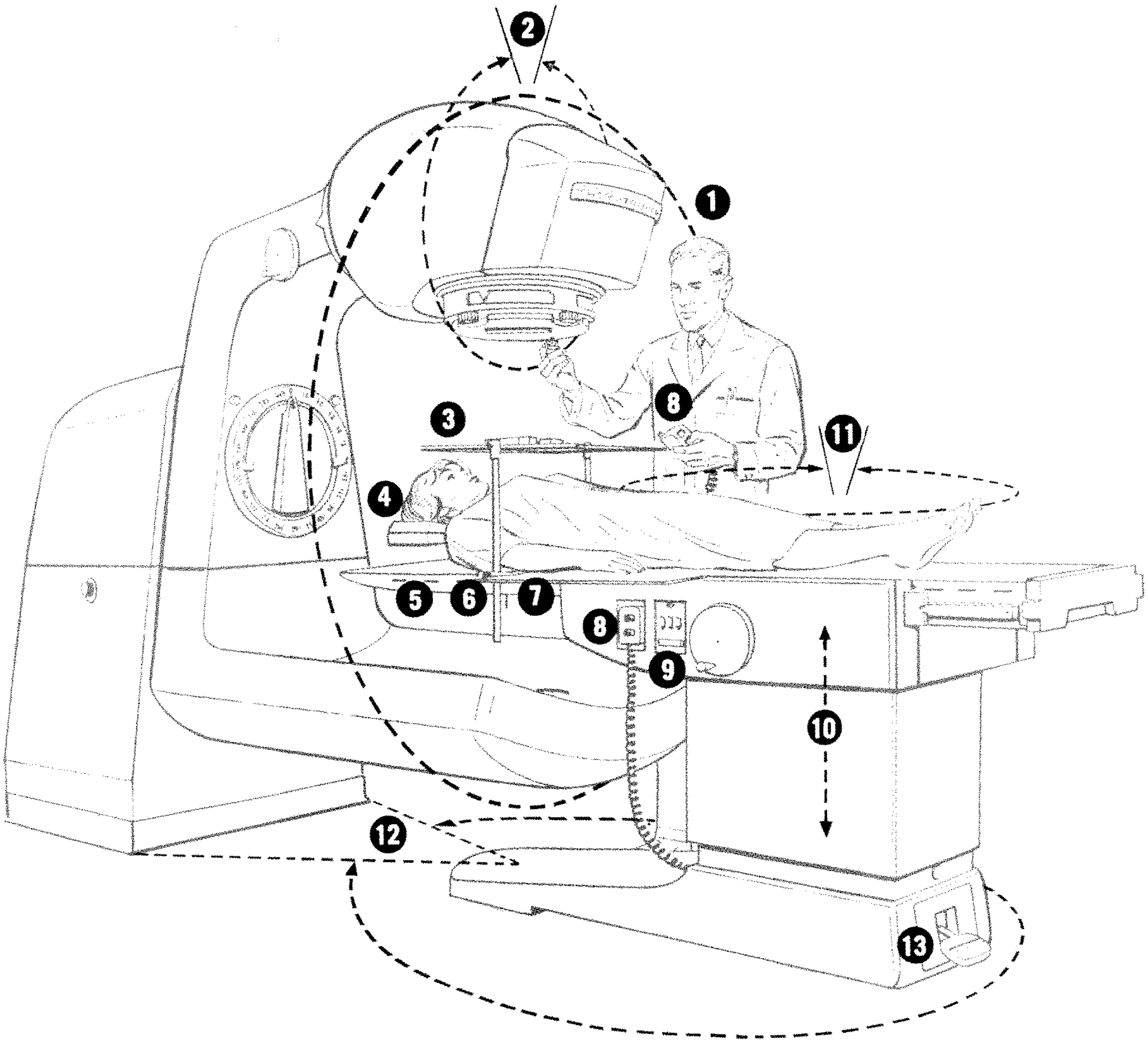

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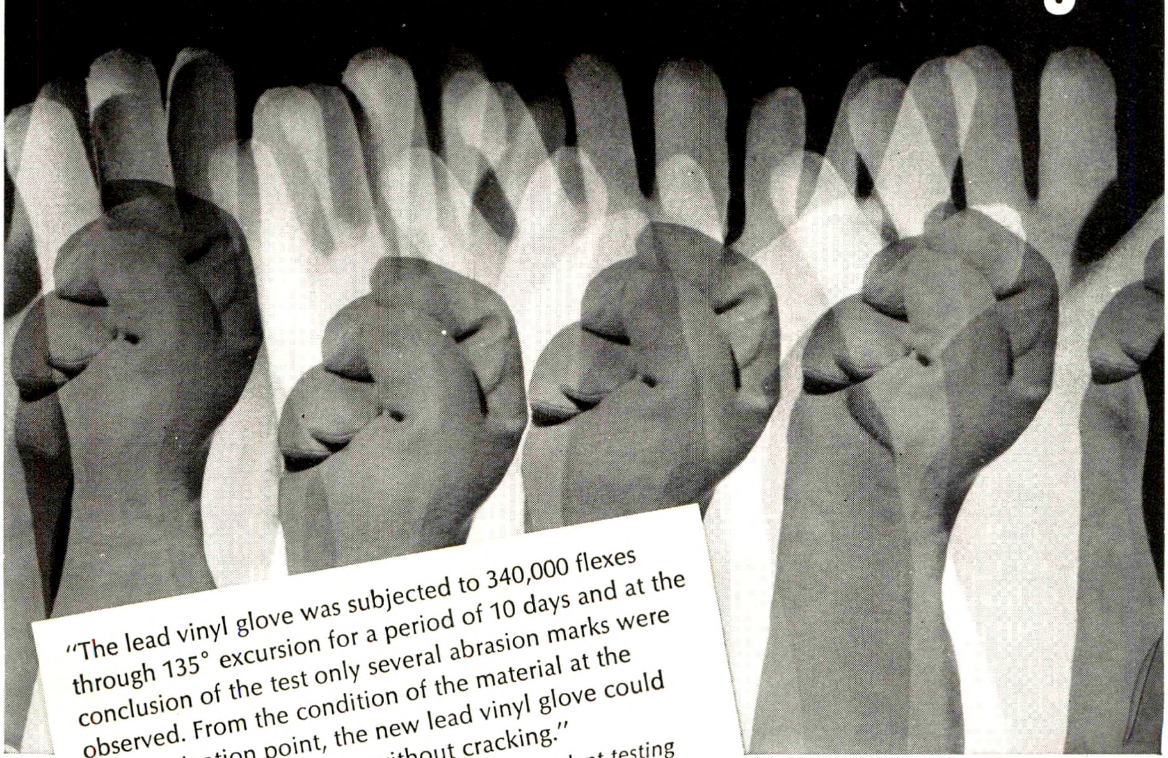
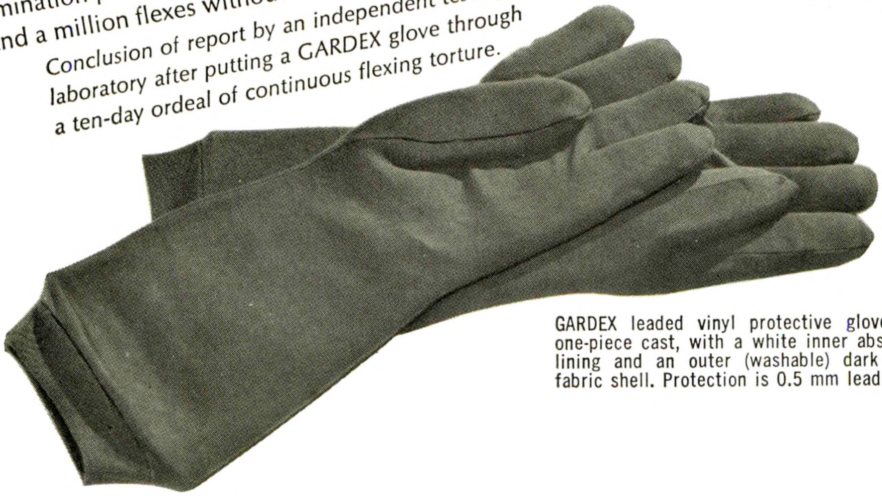


"The lead vinyl glove was subjected to 340,000 flexes through 135° excursion for a period of 10 days and at the conclusion of the test only several abrasion marks were observed. From the condition of the material at the test termination point, the new lead vinyl glove could withstand a million flexes without cracking."

Conclusion of report by an independent testing laboratory after putting a GARDEX glove through a ten-day ordeal of continuous flexing torture.



GARDEX leaded vinyl protective gloves are one-piece cast, with a white inner absorbent lining and an outer (washable) dark green fabric shell. Protection is 0.5 mm lead equiv.

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The supple *flexibility* of a cemented multilayer leadrubber glove *without its frailty*

The protective *certainty* of a seamless "cast-in-one-piece" glove *without its boardlike stiffness*

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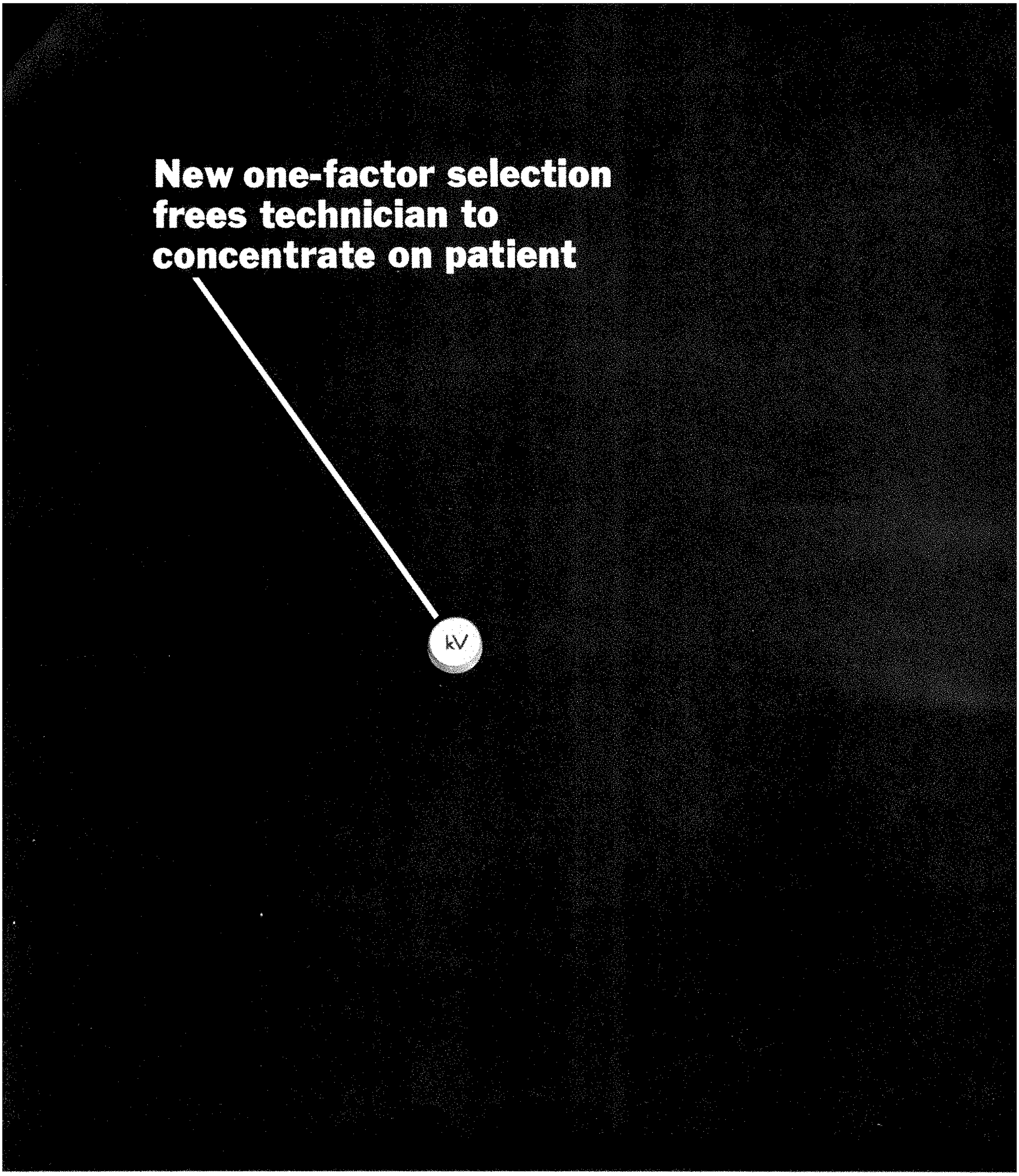

kV is the only factor your technician is required to select. Once that is done, she presses the exposure button and the automatic system does the rest.

Proper density is guaranteed by the Amplimat, the automatic ionization-type exposure control which measures the average X-ray quantum acting on the film over several selectable areas. To ensure positive positioning, the lightbeam indicator projects the location of the measuring areas on the patient. Just as in the case of the modern camera, automatic exposure with Amplimat pays off in consistent production of optimum radiographs.

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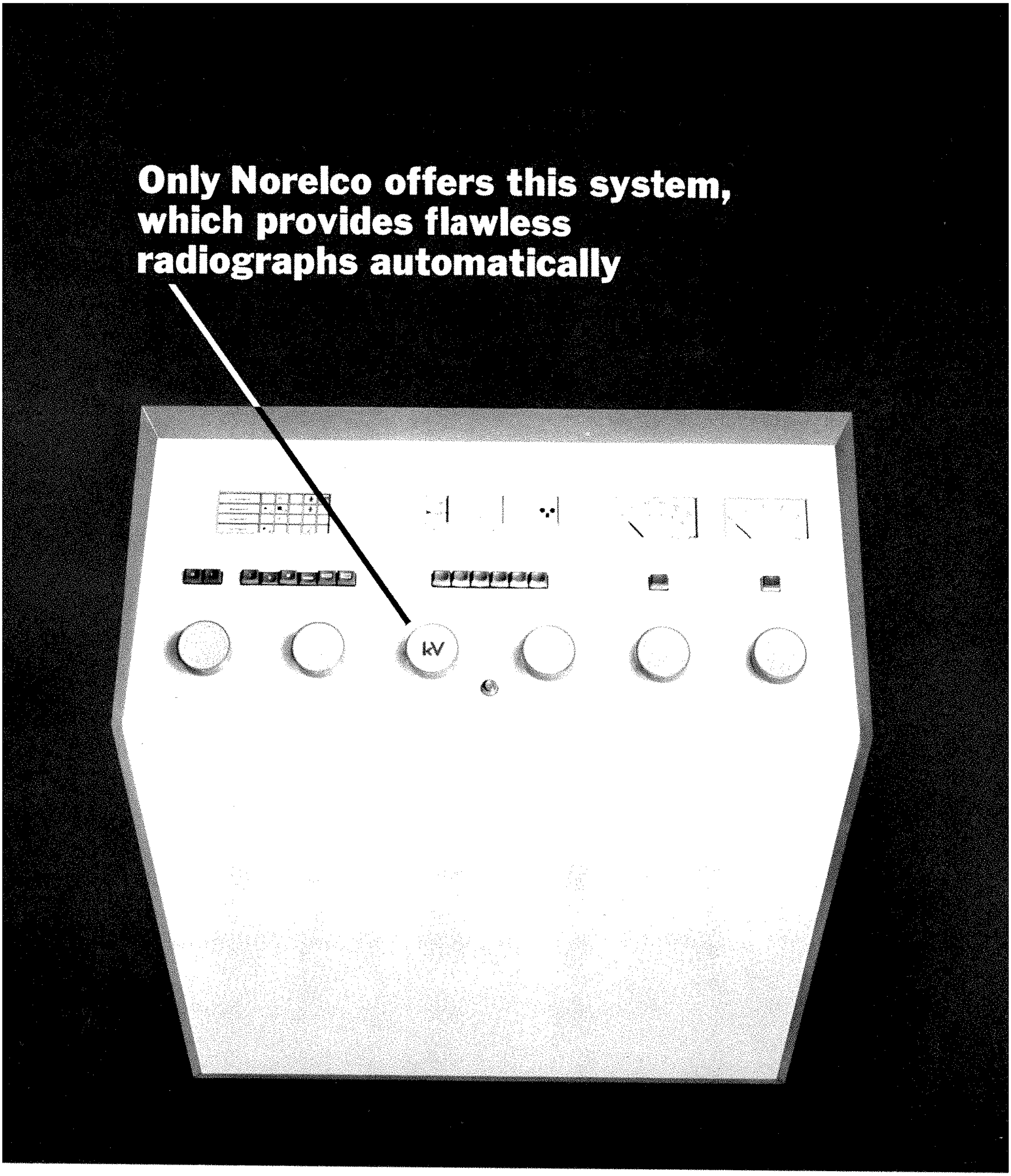
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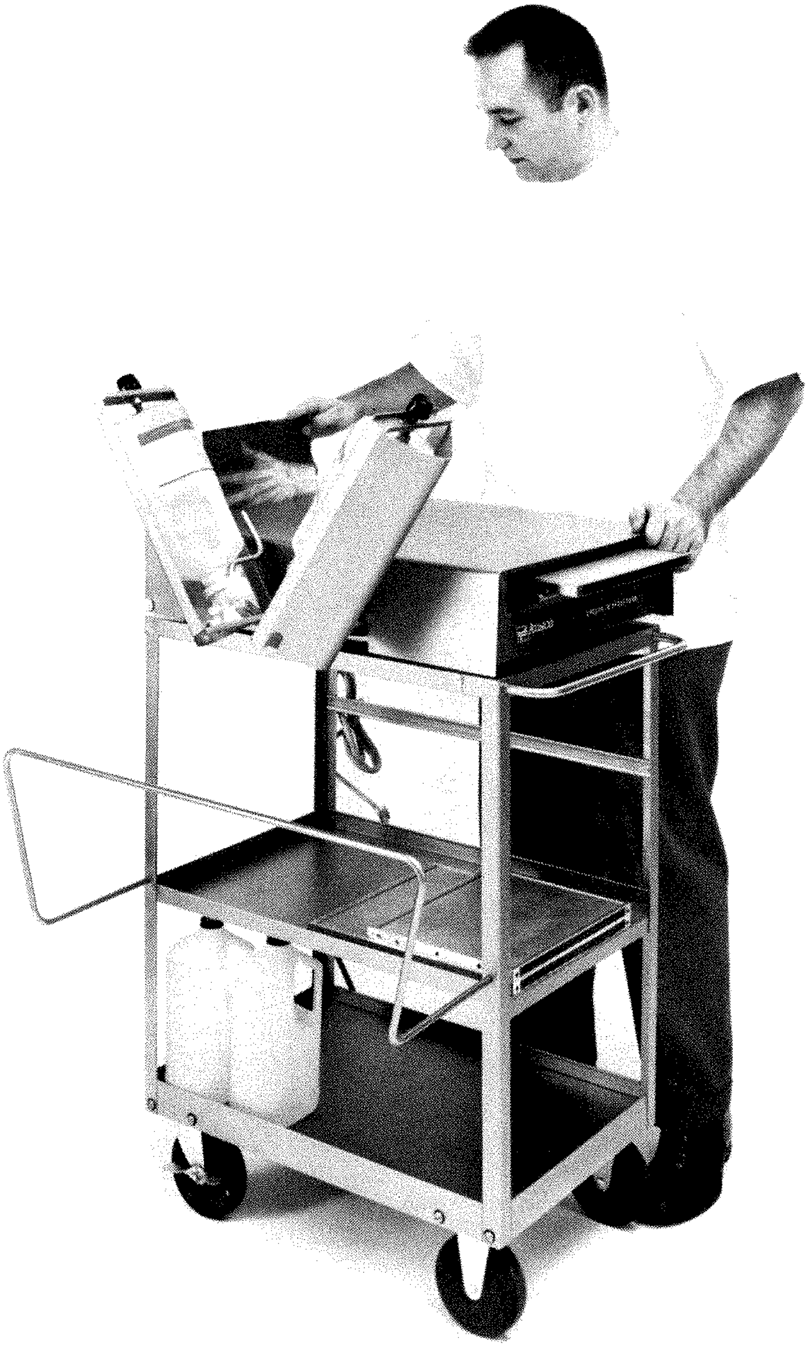

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A processed radiograph ready for viewing in less than a minute! That's the amazingly fast processing time of the Speed-X 'R' Processor.

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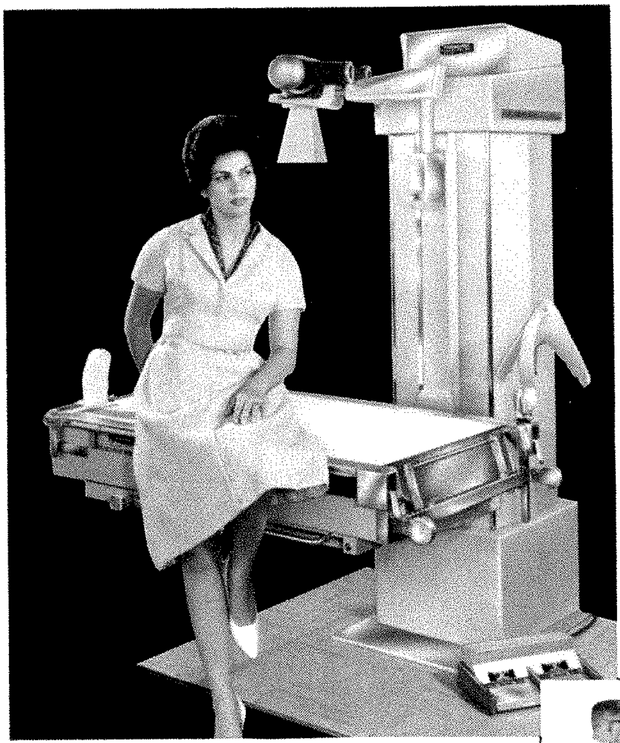

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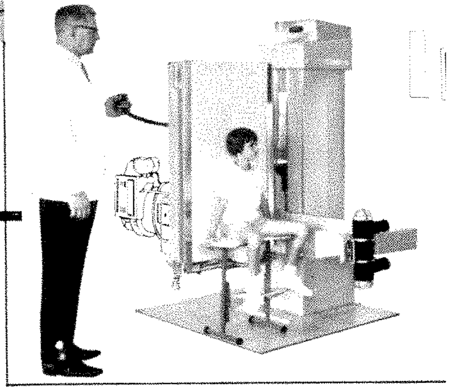

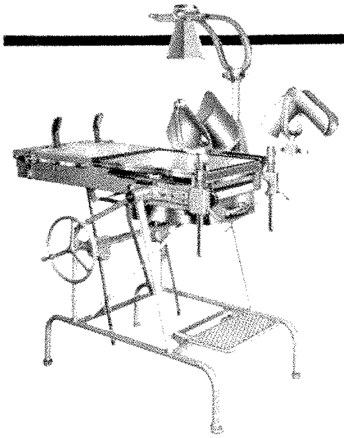

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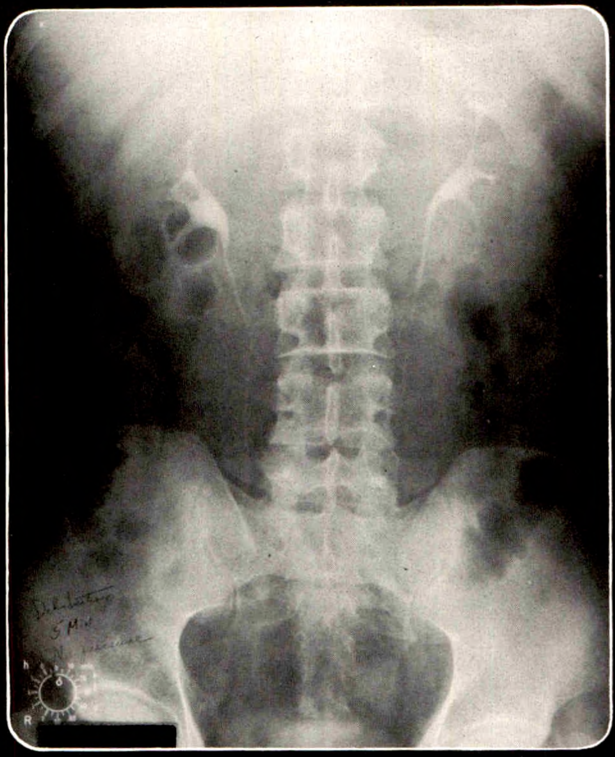

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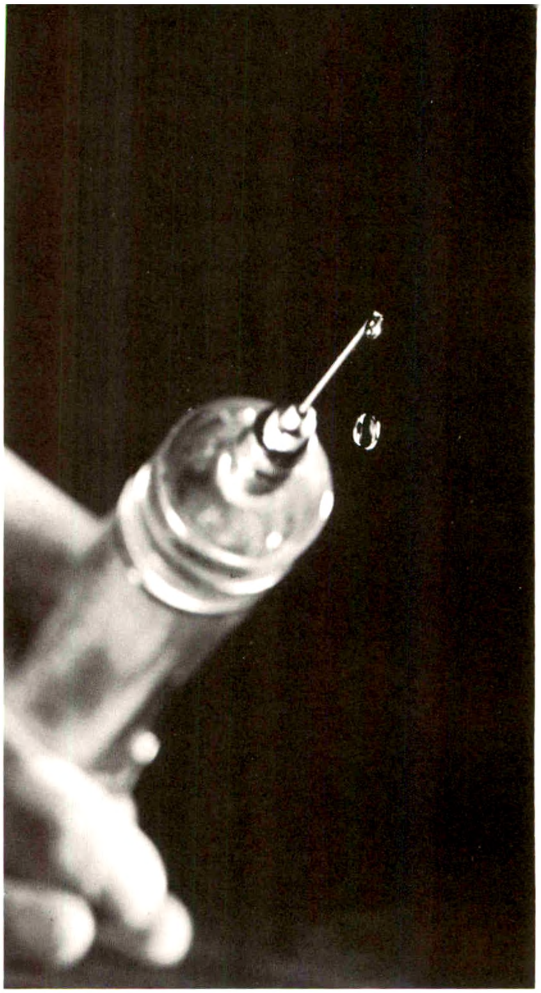
(28.2% iodine)



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CONRAY®

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for intravascular angiocardiography and aortography

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[Sodium Iothalamate 66.8%]

for intravenous urography, intravascular angiocardiography and aortography

Product Particulars

CONRAY: Each ml. contains 0.6 Gm. meglumine iothalamate; not more than 0.11 mg. calcium disodium ethylenediaminetetraacetate as stabilizer; not more than 0.15 mg. sodium biphosphate as a buffer.

Angio-CONRAY: Each ml. contains 0.8 Gm. sodium iothalamate; not more than 0.135 mg. calcium disodium ethylenediaminetetraacetate as stabilizer; not more than 0.15 mg. sodium biphosphate as a buffer.

CONRAY-400: Each ml. contains 0.668 Gm. sodium iothalamate; not more than 0.135 mg. calcium disodium ethylenediaminetetraacetate as stabilizer; not more than 0.15 mg. sodium biphosphate as a buffer.

Side Effects: With CONRAY (meglumine iothalamate 60%) these have been minor and infrequent, and include nausea, vomiting, urticaria. However, as with any iodinated intravascular contrast agent, the possibility of severe reactions exists (neurological complications, the so-called anaphylactic response and cardiovascular collapse). With Angio-CONRAY (sodium iothalamate 80%) and CONRAY-400 (sodium iothalamate 66.8%) rapid injection has produced a wave of warmth or heat passing over the body, often associated with flush. Other transient reactions infrequently observed are nausea, vomiting and bitter taste. In rare instances, injection of a contrast medium has been reported to produce more serious reactions including fatalities. **Note:** Because of the possibility of severe reactions to any medium, patients should not be left alone for at least 15 minutes following injection.

Caution: CONRAY-400 (sodium iothalamate 66.8%) and Angio-CONRAY (sodium iothalamate 80%) are not intended for use in cerebral angiography. For this purpose, CONRAY (meglumine iothalamate 60%) is recommended.

Contraindications: For all three media, caution is required in cases involving severe systemic disease. In patients with advanced renal disease, use with caution and then only when need for examination dictates. In patients with a history of allergy or those exhibiting a positive reaction to the sensitivity test, drugs and facilities for emergency use must be readily available.

Precautions: For Angio-CONRAY (sodium iothalamate 80%) and CONRAY-400 (sodium iothalamate 66.8%), cardiac arrhythmias, including ventricular fibrillation, have been reported with the use of these media in procedures for visualizing the heart and its associated large vessels. Such occurrences may be associated with situations in which appreciable amounts of relatively undiluted medium enter the coronary circulation. Facilities for immediate treatment of such reactions should be available.

Product Bibliography

1. Marshall, T. R., and Ling, J. T.: Am. J. Roentgenol. *89*:423 (Feb.) 1963. 2. Dotter, C. T., *et al.*: Northwest Med. *61*:41 (Jan.) 1962. 3. Steinberg, I., and Evans, J. A.: Radiology *79*:395 (Sept.) 1962. 4. Smolik, E. A., and Nash, F. P.: Missouri Med. *59*:863 (Sept.) 1962. 5. Marshall, T. R.; Ling, J. T., and Gonzalez, R.: Radiology *81*:568 (Oct.) 1963. 6. Hinck, V. C., and Dotter, C. T.: J. Neurosurg. *19*:312 (April) 1962. 7. Bernstein, E. F., *et al.*: Surgery *51*:663 (May) 1962. 8. Kanick, V., and Finby, N.: Radiology *80*:438 (March) 1963. 9. Straube, K. R., and Dotter, C. T.: Scientific Paper Presented before 11th Internat. Cong. European Soc. Cardiov. Surg., Stockholm, Sweden, July, 1962. 10. Foster, J. H., *et al.*: Scientific Exhibit at 111th Annual Meet. A.M.A., Chicago, Illinois, July, 1962. 11. Foster, J. H., *et al.*: JAMA *182*:1009 (Dec. 8) 1962. 12. Sessions, R. T., *et al.*: Surg. Gynec. & Obst. *115*:187 (Aug.) 1962.

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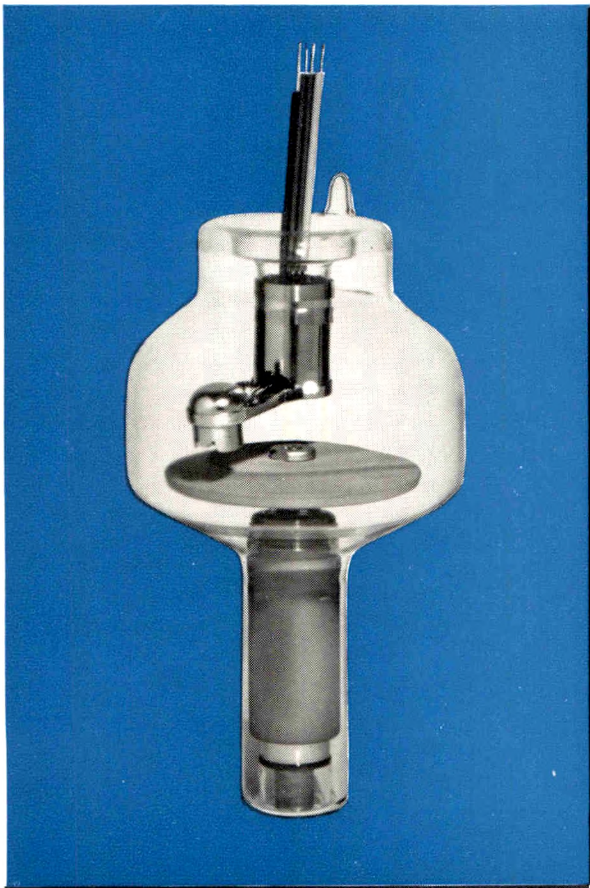

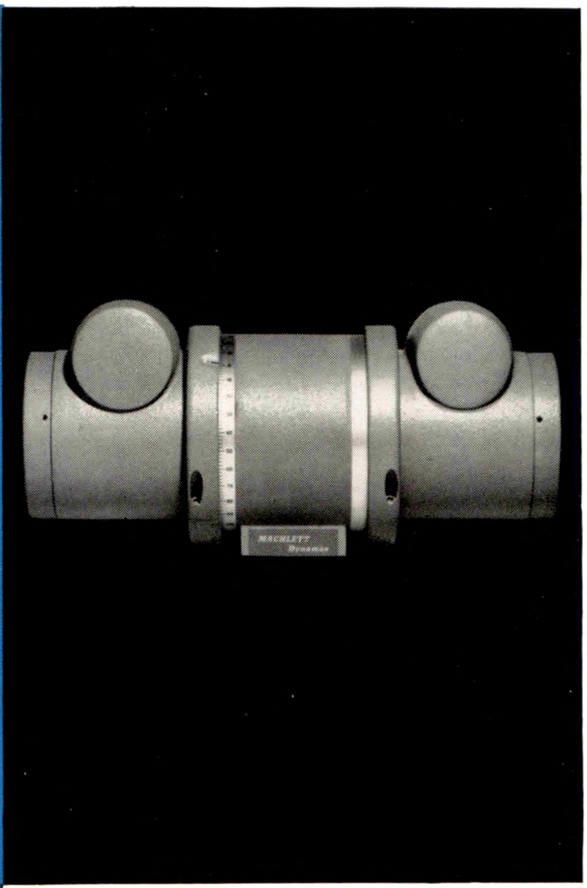

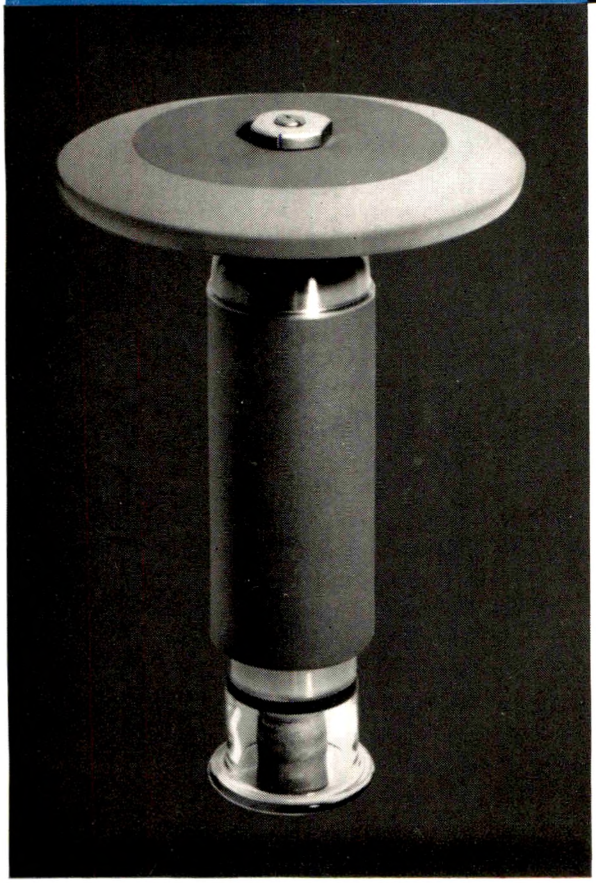

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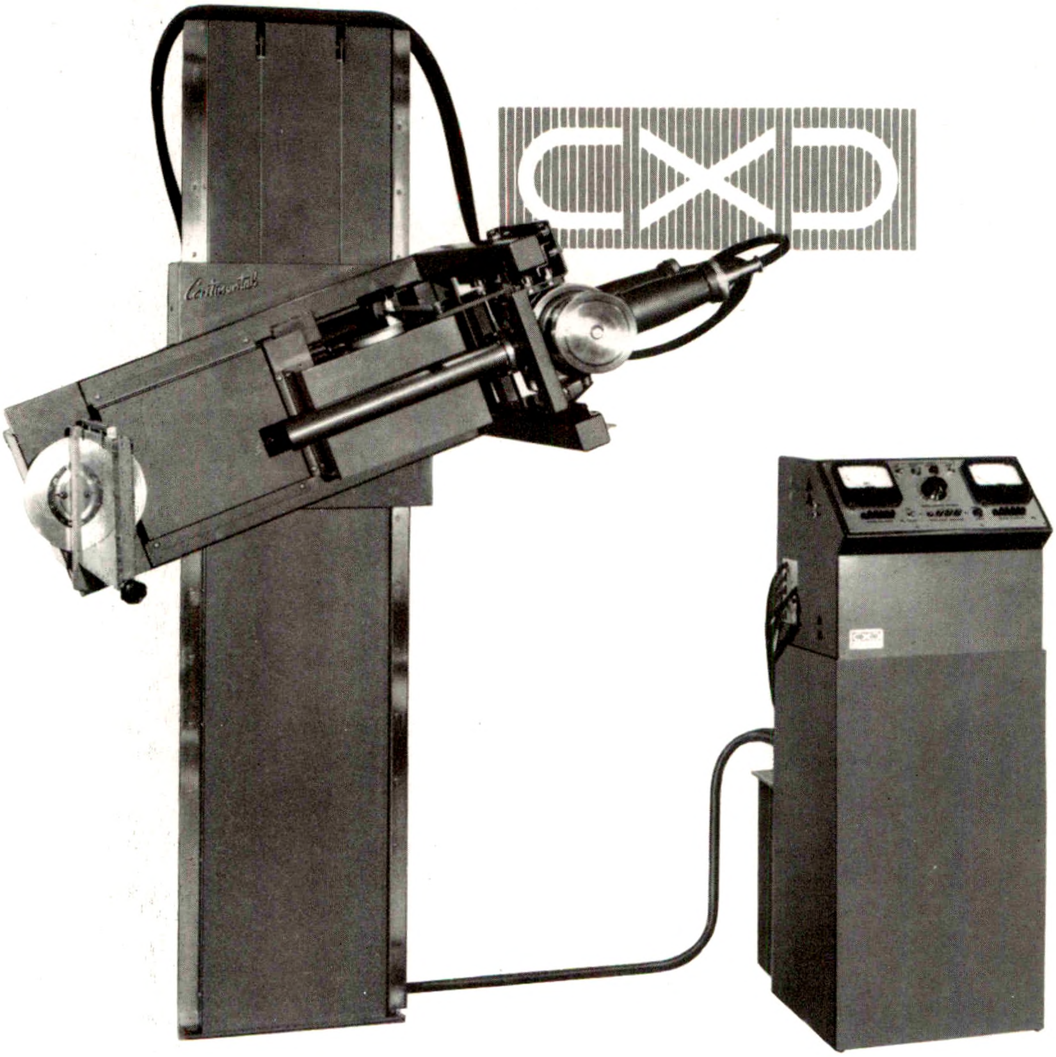

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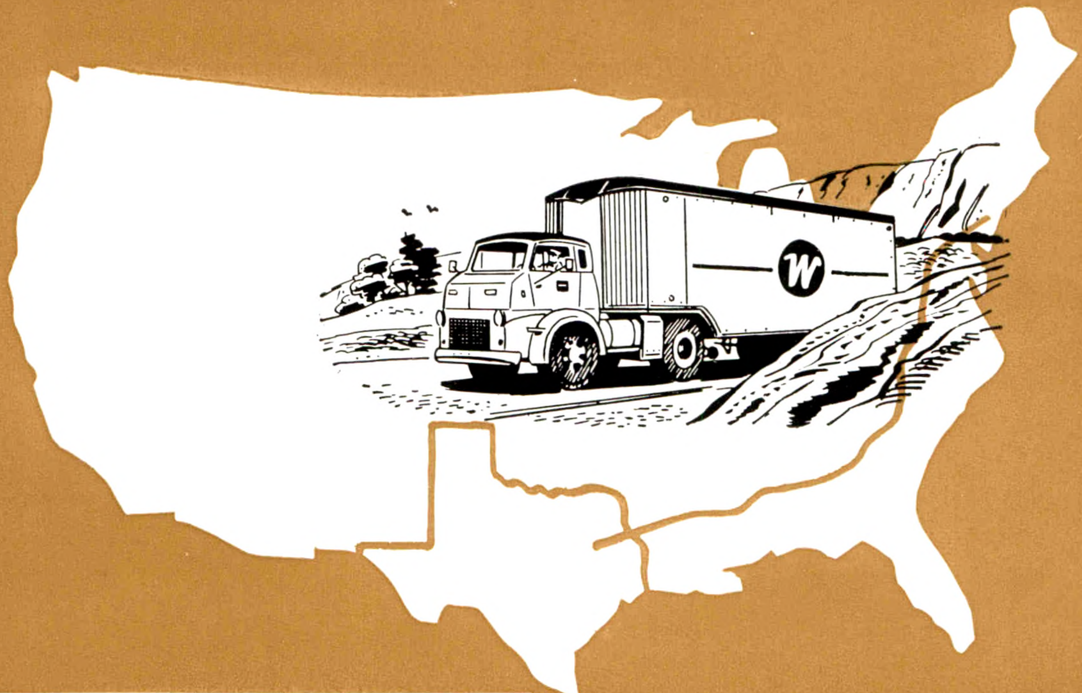

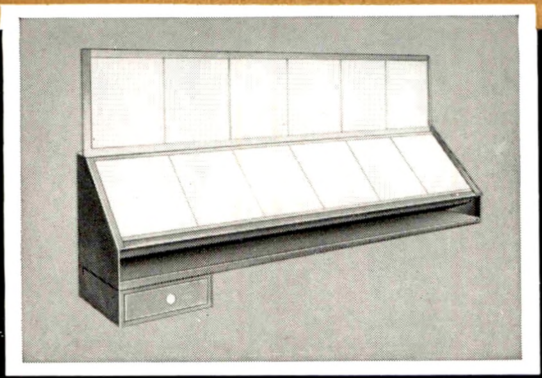

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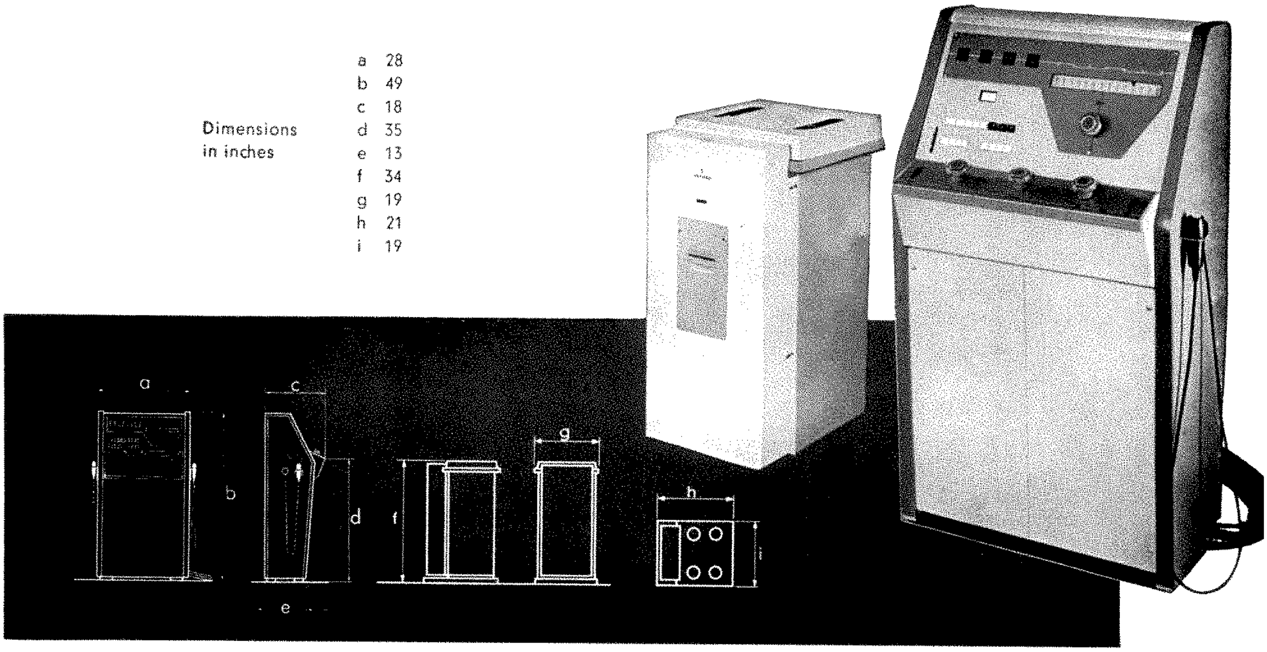

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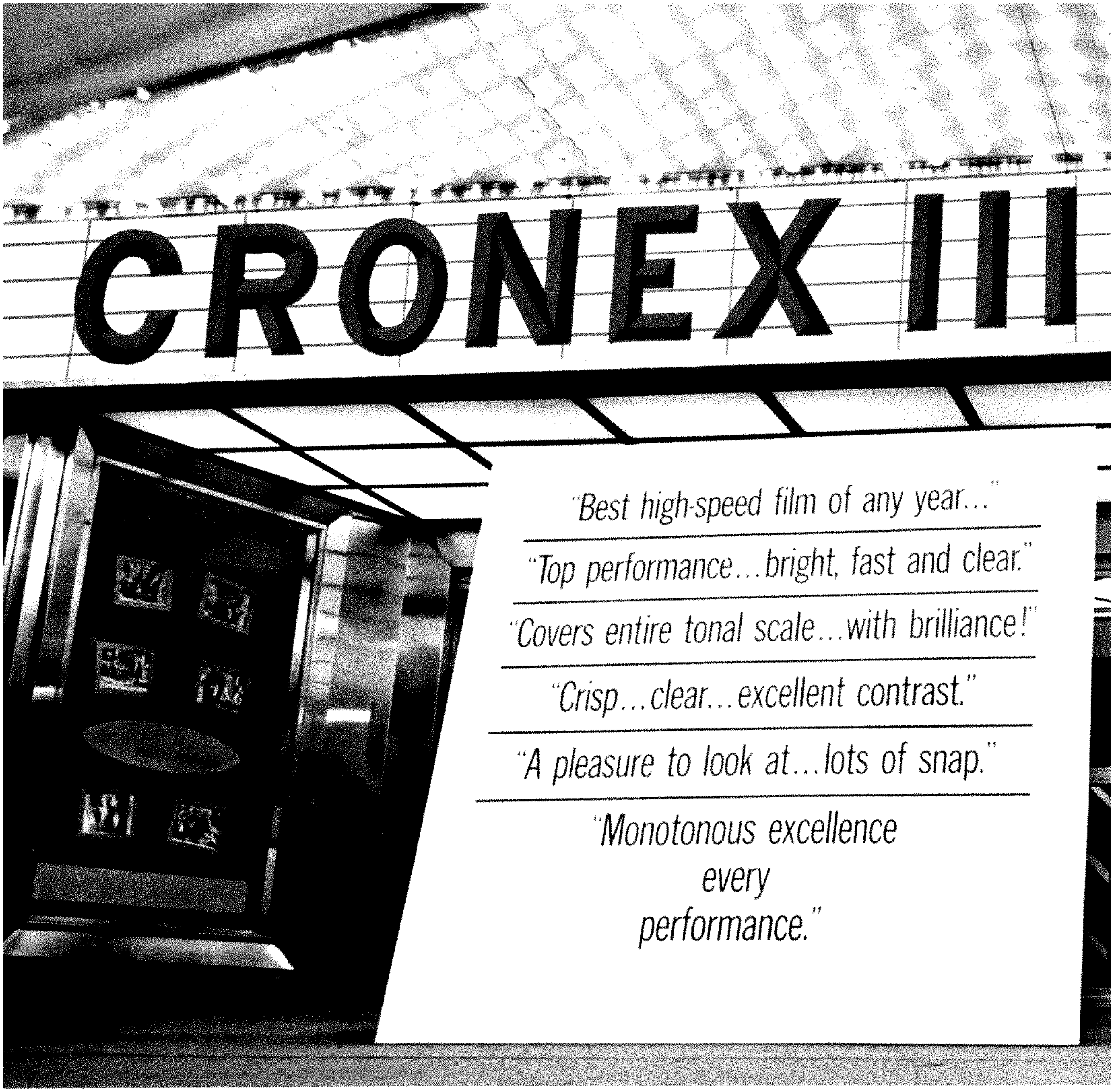

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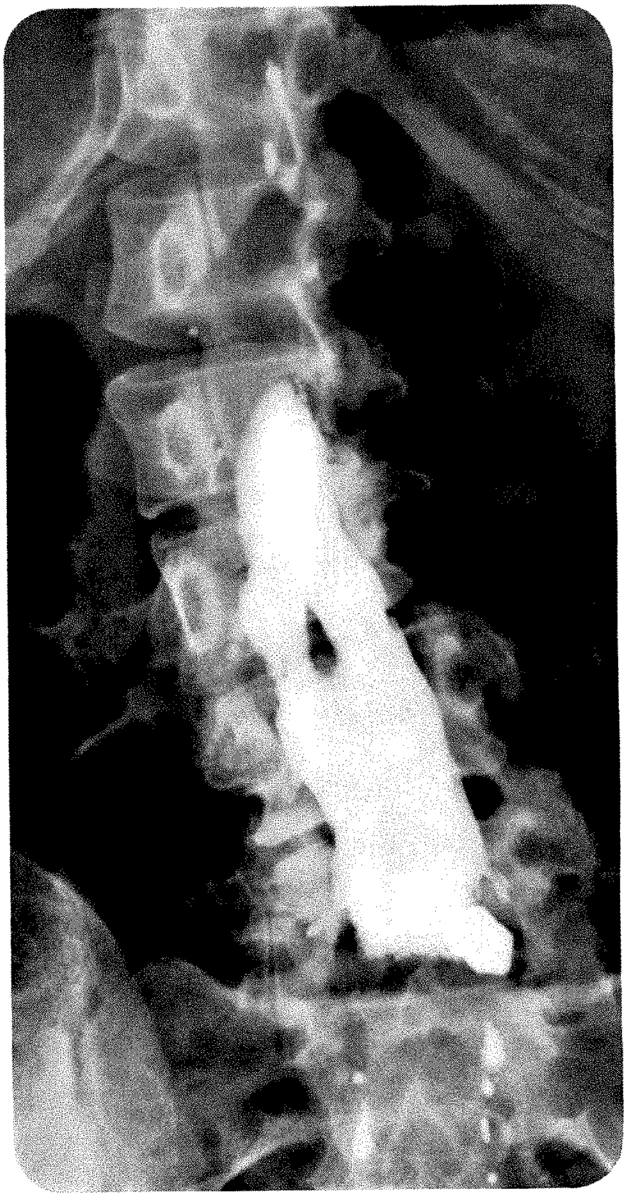

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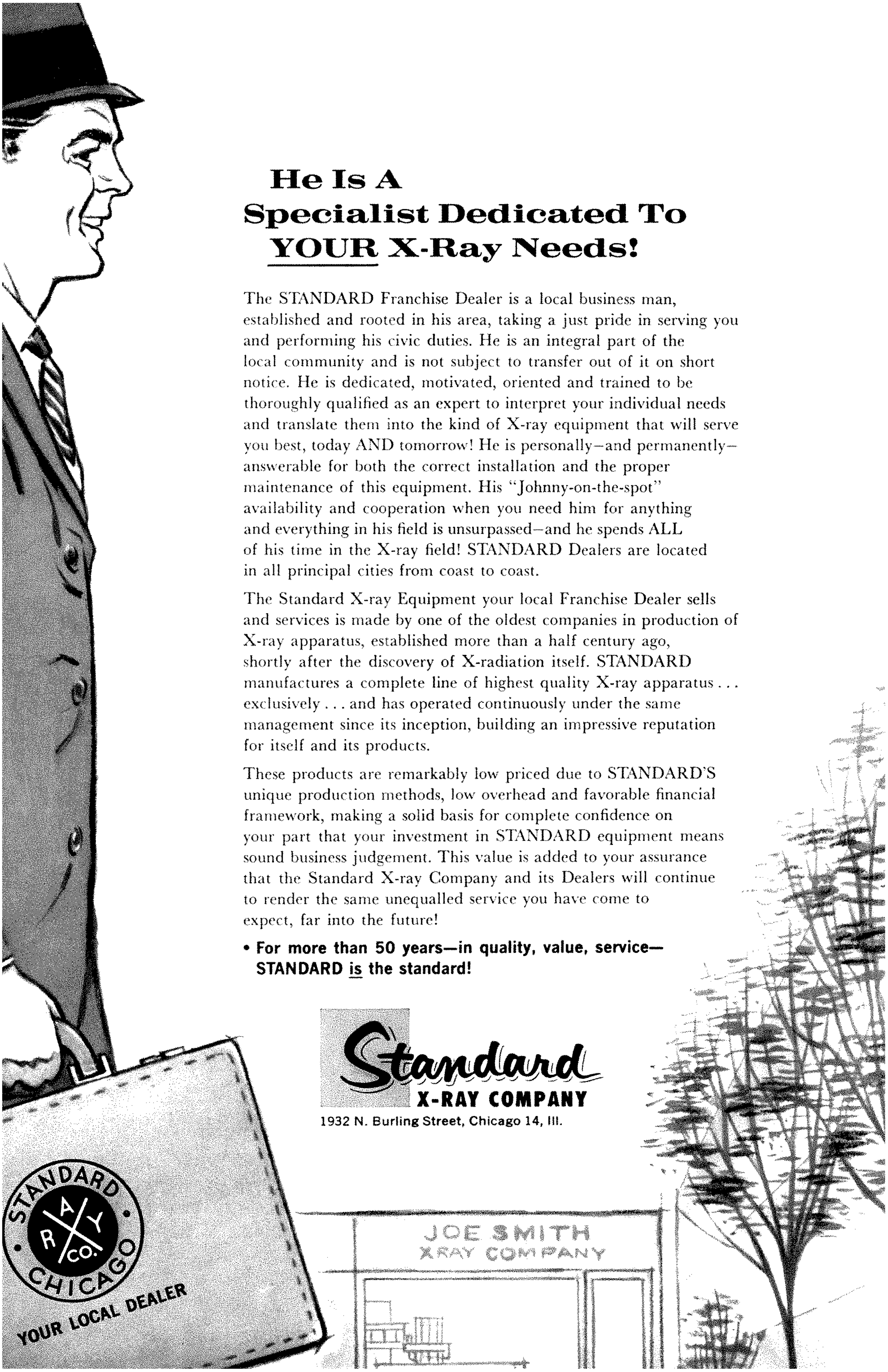

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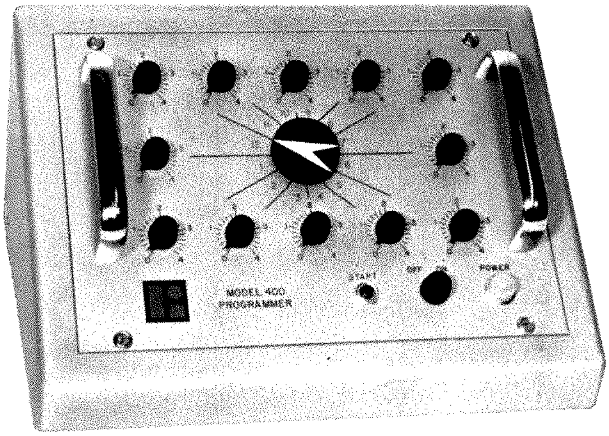

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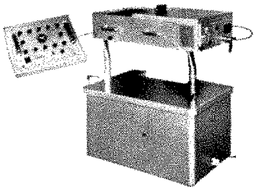

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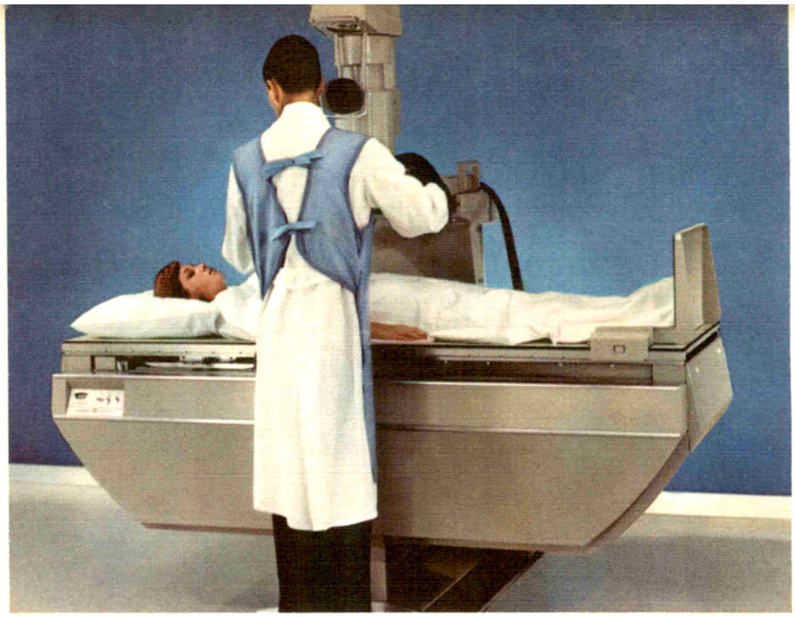

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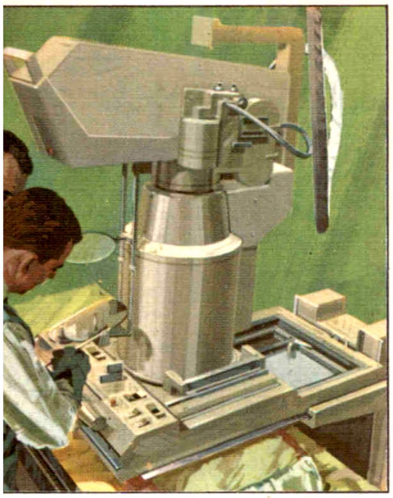

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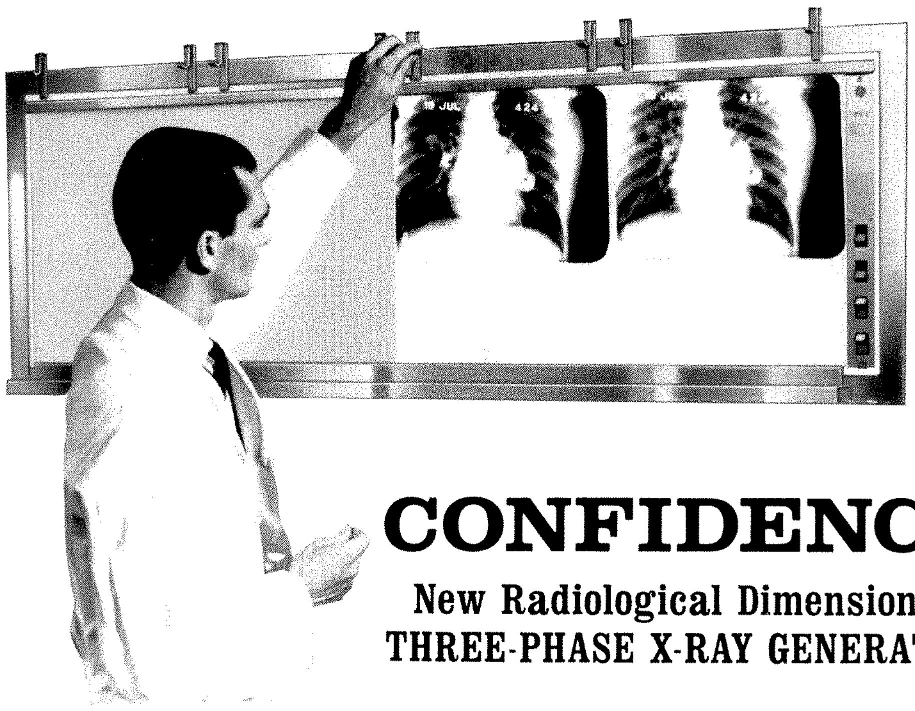

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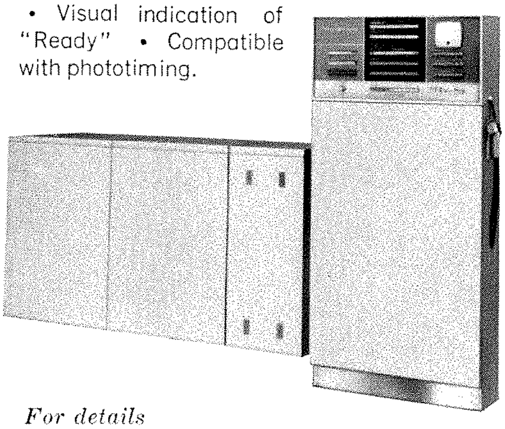

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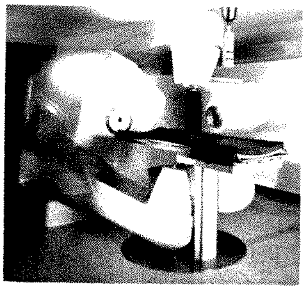

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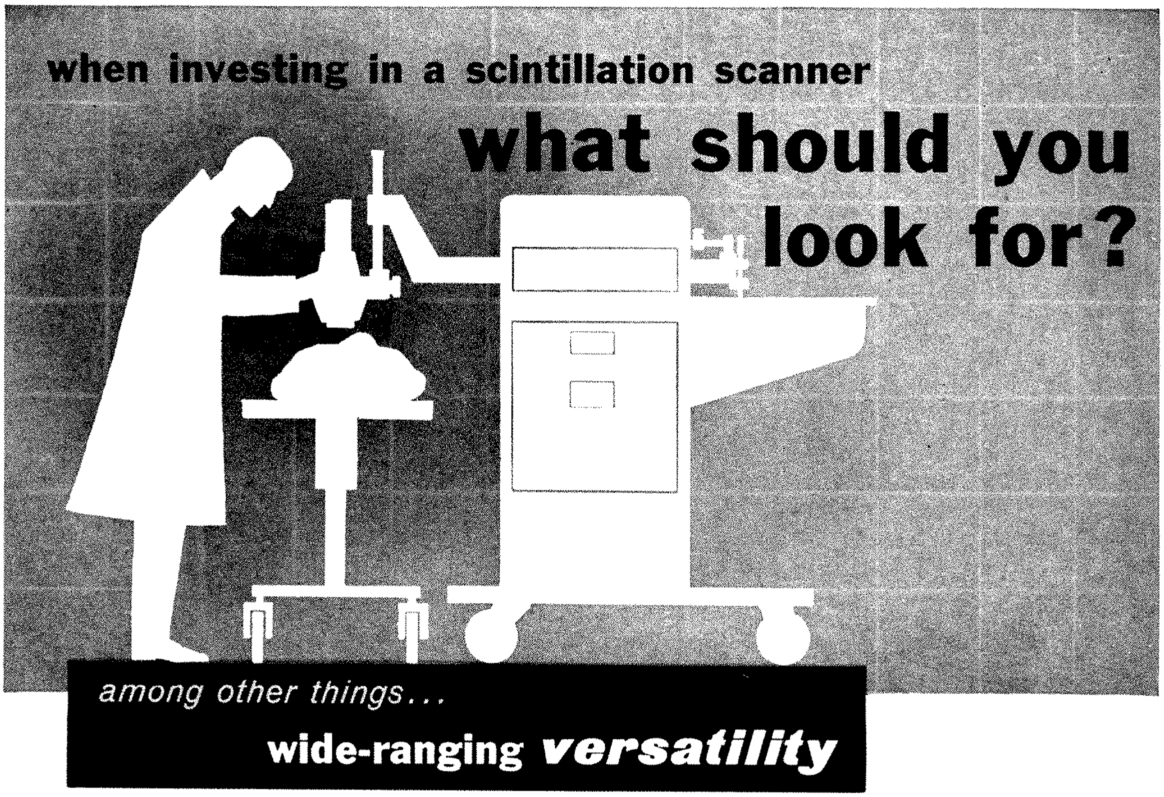
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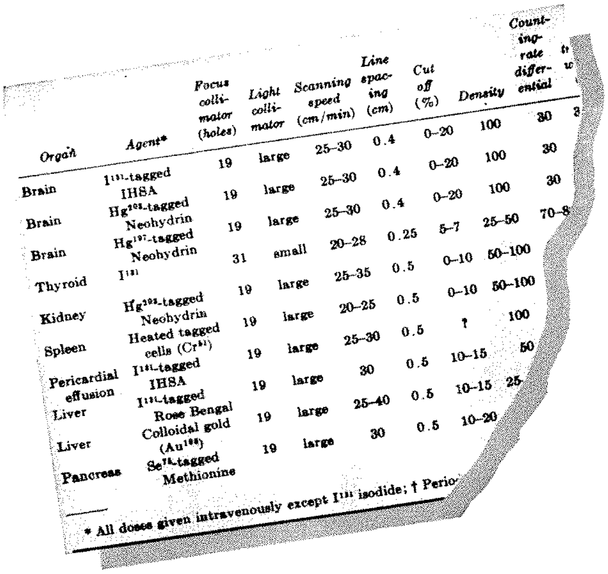
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Brain	Hg^{197}-tagged Neohydrin	19	large	25–30	0.4	0–20	100	30
Thyroid	I^{131}	31	small	20–28	0.25	5–7	25–50	70–8
Kidney	Hg^{203}-tagged Neohydrin	19	large	25–35	0.5	0–10	50–100	
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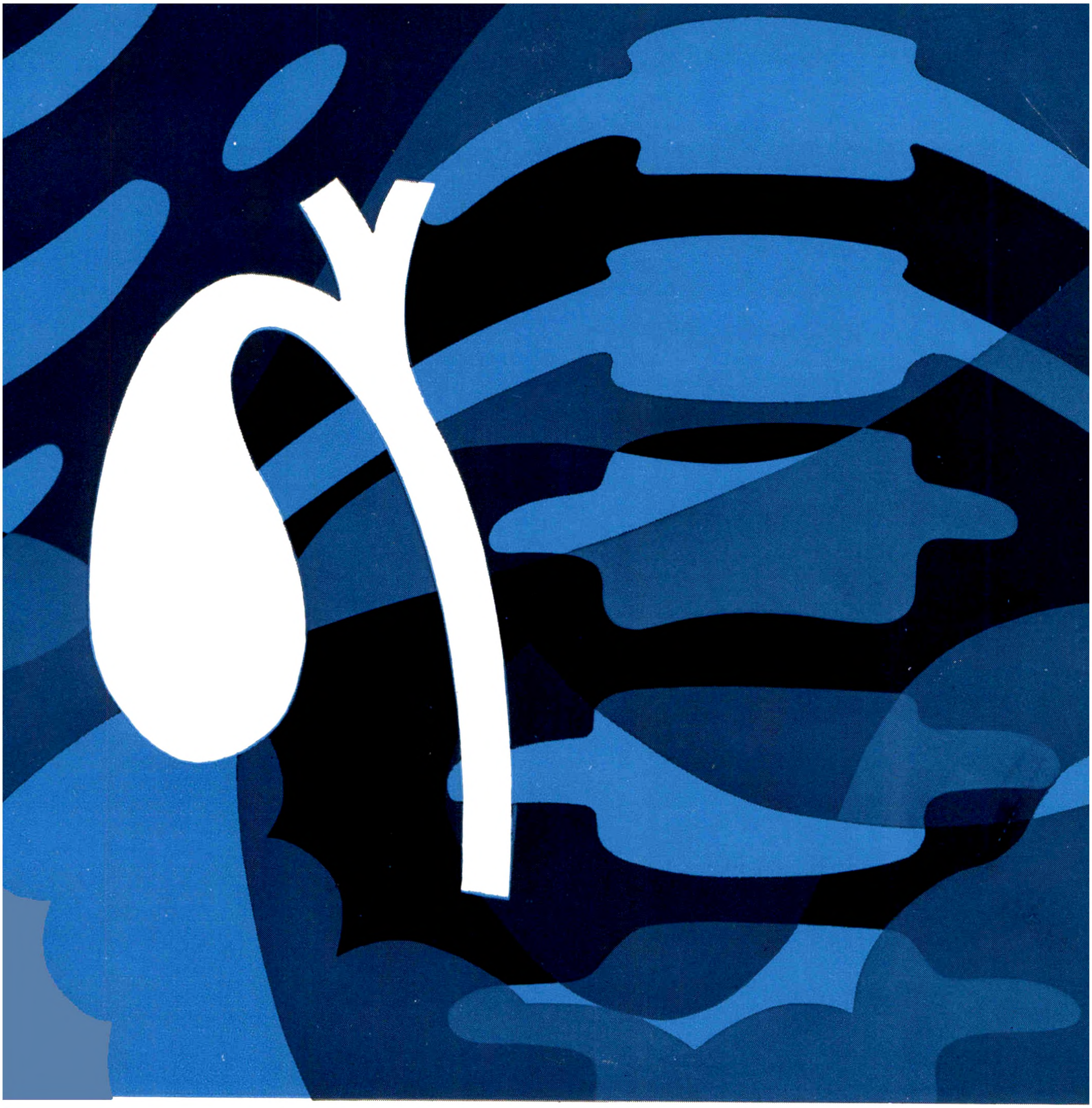

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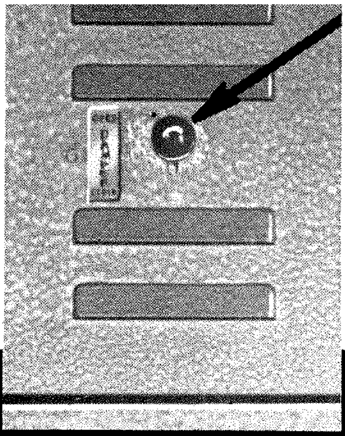

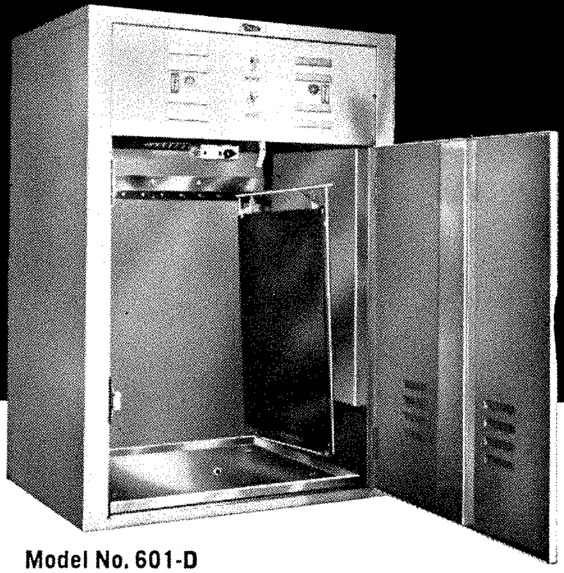

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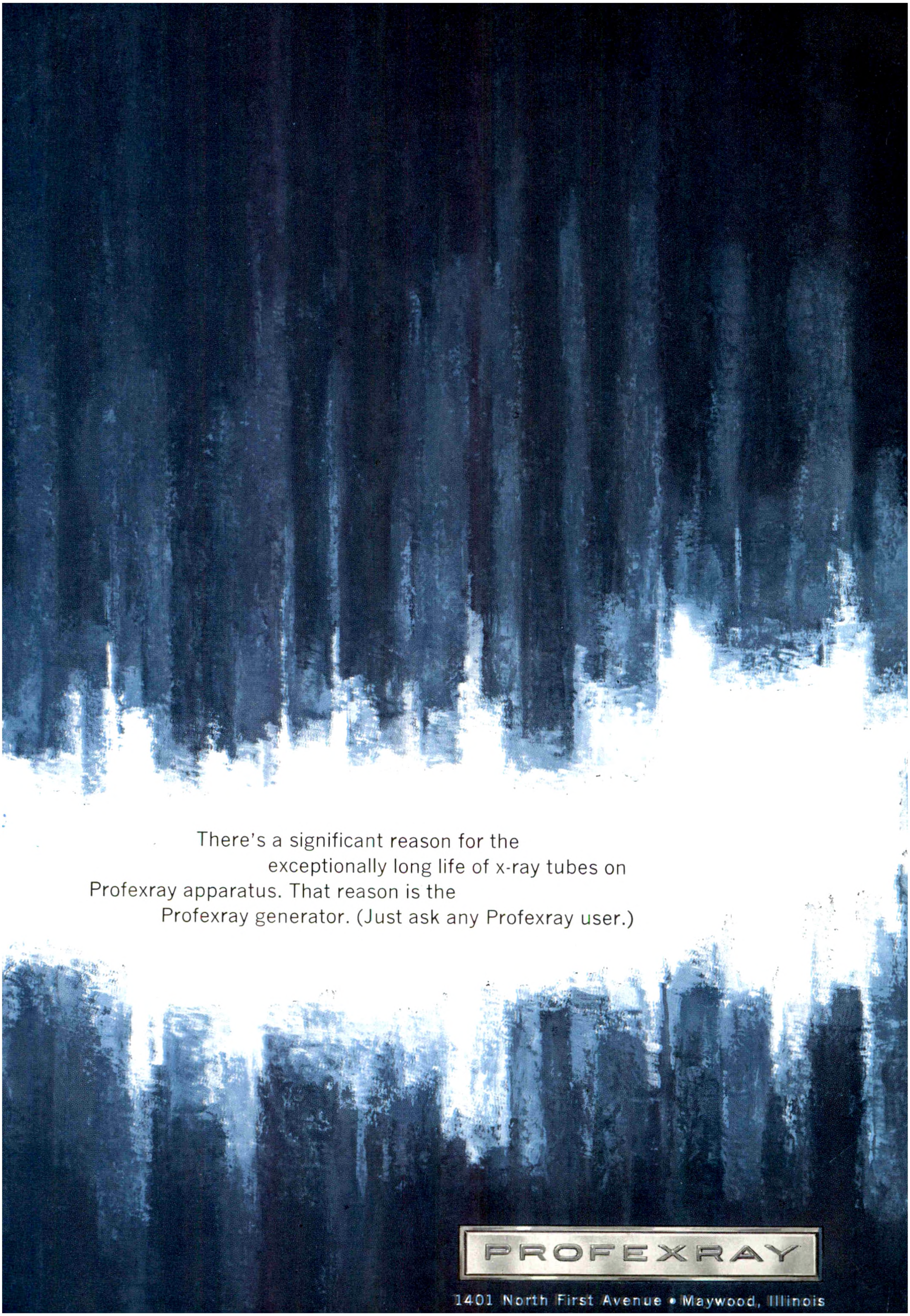

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ROENTGENOGRAPHIC FEATURES IN CASES WITH ORIGIN OF BOTH GREAT VESSELS FROM THE RIGHT VENTRICLE WITHOUT PULMONARY STENOSIS*

By LEWIS S. CAREY, M.D., *and* JESSE E. EDWARDS, M.D.
ST. PAUL, MINNESOTA

ORIGIN of both great vessels from the right ventricle without pulmonary stenosis is an uncommon cardiac malformation to which various names such as "double outlet right ventricle," "partial transposition" and "Taussig-Bing complex" have been applied. Cases exhibiting the combination of anomalies which allows such a designation were separated anatomically by Neufeld and associates[6] into two types on the basis of the position of the ventricular septal defect, which was present in each case.

ANATOMIC CLASSIFICATION

According to the anatomic classification of these authors, Type I is characterized by a ventricular septal defect situated immediately *below the crista supraventricularis*, which forms the superior and anterior margin of the defect. The junction of the anterior mitral leaflet and the septal tricuspid leaflet forms the posterior wall of the defect. In contrast to the normal heart, in the classic varieties of the malformation there is discontinuity between the anterior leaflet of the mitral valve and the aortic valvular tissue. The internal relationships of the great vessels are abnormal. The aorta does not extend caudad to the left and posteriorly to a position of normal origin from the left ventricle; instead, it originates entirely from the right ventricle and extends vertically upward. From the frontal aspect, the aortic root lies to the right of the pulmonary trunk; from the lateral aspect, the proximal portion of the ascending aorta is more anteriorly placed than is normal (partially transposed) and lies near the same sagittal plane as the proximal part of the pulmonary trunk. The anterior wall of the pulmonary trunk, however, is usually slightly anterior to the anterior wall of the aorta. The aortic orifice occupies a position

---

* From the Department of Radiology, St. Joseph's Hospital, St. Paul, Minnesota; the Department of Pathology, The Charles T. Miller Hospital, St. Paul, Minnesota and the Departments of Radiology and Pathology, University of Minnesota, Minneapolis, Minnesota.

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above the parietal limb of the crista supraventricularis and is in front of the tricuspid valve. The aortic valve is in the same coronal body plane as the pulmonary valve, a feature of diagnostic significance which is usually readily discernible on angiocardiographic studies.

Clinically and hemodynamically, there is a resemblance to ventricular septal defect associated with pulmonary hypertension. A systolic murmur without cyanosis is the common finding. Cyanosis of mild degree may be present on occasion; however, when encountered, it should suggest the presence of an additional cardiac malformation or the presence of complicating obstructive pulmonary vascular disease.

Associated anomalies may be present. These include coarctation of the aorta, malformations of the mitral valve, supravalvular stenosing ring of the left atrium, systemic and pulmonary venous anomalies, patent ductus arteriosus and persistent common atrioventricular canal. In some cases which functionally resemble the classic form of Type I of the malformation, there are anatomic variants which collectively are herein to be considered as atypical forms of Type I.

Type II is characterized by the presence of a large ventricular septal defect which lies *above the septal limb of the crista supraventricularis* and immediately below the pulmonary valve. The classic examples were classified as Type IIA by Neufeld and associates and are synonymous with the Taussig-Bing complex. In a rare case the ventricular septal defect may also extend beneath the aortic valve to constitute Type IIB.

Clinically, patients with the Type II malformation exhibit cyanosis, usually moderate to severe in degree, from birth or early infancy and a systolic murmur indistinguishable from that observed in the usual examples of large ventricular septal defect.

There are rare forms of transposition of the great vessels which have certain clinical, pathologic and roentgenographic similarities to Type II and yet certain differences. Two such cases are presented in this report to emphasize the similarity of roentgenographic and angiocardiographic findings that may occur in cases of origin of both great vessels from the right ventricle and anatomically related conditions.

In addition to the typical examples of either Types I or II of origin of both great vessels from the right ventricle, there are other instances of malformation in which, while both vessels arise from the right ventricle, the anatomic pattern does not closely conform to either of the two aforementioned types. Two such cases are presented as atypical examples without specific reference to either Type I or Type II.

This study comprises 13 cases of origin of both great vessels from the right ventricle without pulmonary stenosis. Emphasis is placed on the roentgenographic and angiocardiographic findings. Pathologic observations, where present, are summarized for the purpose of correlation with the roentgenologic studies.

Of the 13 patients, 10 died and necropsy was performed in each. Four of these latter cases were among the 10 which formed the basis for the anatomic study of Neufeld and associates.[6]

Additionally, as mentioned, 2 cases with other conditions will be presented for comparison with Type II cases.

CLASSIC TYPE I

ANATOMICALLY PROVED (2 CASES)

Roentgenologic Observations.

Case 1. Male, aged 3 months. (Case 5 of Neufeld and associates.[6])

Roentgenograms of the thorax (Fig. 1*a*) showed moderate cardiomegaly, enlargement of the right ventricle and left atrium and minimal prominence of the central pulmonary vasculature.

Angiocardiographic study (Fig. 2) consisted of selective right ventriculography done through a catheter advanced from the right atrium. The lateral view showed simultaneous opacification of both great vessels

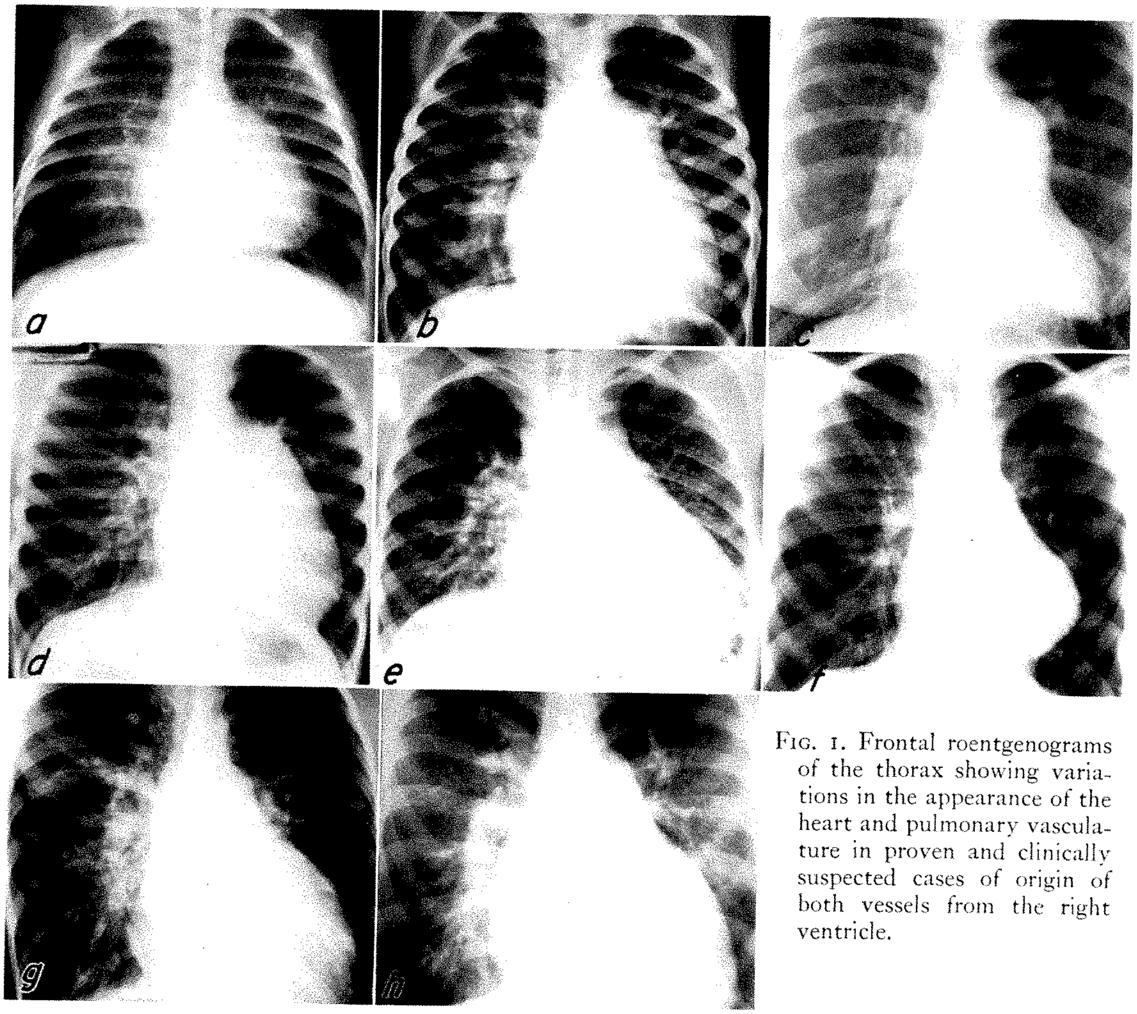


Fig. 1. Frontal roentgenograms of the thorax showing variations in the appearance of the heart and pulmonary vasculature in proven and clinically suspected cases of origin of both vessels from the right ventricle. Type I—typical and atypical forms. (*a*) Case I, male, 3 months. (*b*) Case V, male, 10 years. (*c*) Case III, female, 27 years. (*d*) Case IV, female, 8 years. (*e*) Case VII, female, 9 years. (*f*) Case VI, male, 10 years. (*g*) Case VIII, male, 16 years. (*h*) Case II, male, 18 years.

from the right ventricle with the pulmonary trunk opacifying more densely than the aorta. The proximal part of the ascending aorta was completely superimposed over the proximal portion of the pulmonary trunk.

Case II. Male, aged 18 years. (Case 3 of Neufeld and associates;[6] case also reported by Lucas and associates.[5])

Roentgenograms of the thorax (Fig. 1*h*) showed features similar to those in Case III (*infra vide*).

Angiocardiographic study (Fig. 4, *a* and *b*) consisted of selective aortography. In frontal view this showed a somewhat foreshortened ascending aorta which appeared to exhibit less curvature than normal. In lateral view the ascending aorta was directed anteriorly throughout its entire course and did not show the normal inclination of the ascending aorta to bend posteriorly as the region of the valve is approached. The aortic valve plane was nearly horizontal in both frontal and lateral views.

Pathologic Observations.

In each of the 2 cases which were classic examples of origin of both great vessels from the right ventricle, Type I, and which

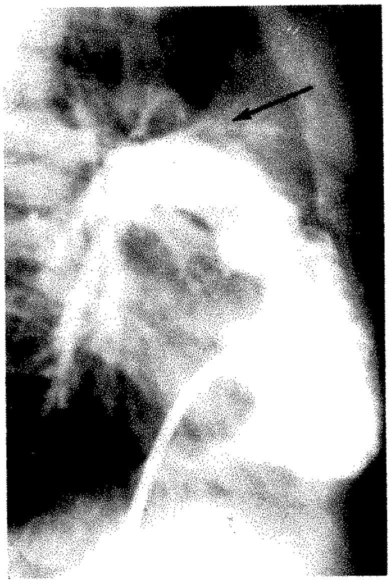


Fig. 2. Case i. Type i. Selective right ventriculogram. Lateral view. Simultaneous opacification of both great vessels. Pulmonary trunk opacified more densely than the aorta. The proximal ascending aorta superimposed over the pulmonary trunk (arrow points to anterior margin of aorta).

were studied at necropsy (Case i and ii), the features as defined by Neufeld and associates[6] were present. No continuity existed between aortic and mitral valvular tissue. Of particular interest to emphasize is that in Case i the upper aspect of the parietal limb of the crista supraventricularis was prominent. Its basal aspect appeared to extend medially from the basal aspect of the anterior wall of the right ventricle to insert into that part of the ventricular septum which lay between the origins of the aorta and pulmonary trunk. This mass of muscle forms the radiolucent "tongue" between the origins of the two great vessels, as may be seen in right ventriculograms.

In Case ii the crista failed to be represented by so prominent a spur.

In each case the ventricular septal defect was sufficiently large as not to be obstructive.

A malformation of the mitral valve, which was considered an Ebstein type of deformity of this valve, was observed in Case i.

CLINICAL CASES (3 CASES)

Among the patients who are living, there were 3 cases in which the results of roentgenologic studies were considered consistent with those of classic Type i. These 3 cases are presented in this section as Case iii, iv and v.

Roentgenologic Observations.

Case iii. Female, aged 27 years.

Roentgenograms of the thorax (Fig. 1*c*) showed moderate cardiomegaly, right ventricular enlargement, striking prominence of the pulmonary trunk, enlargement of the central pulmonary vasculature and a disparity between the size of the central and peripheral pulmonary vasculature, suggesting the presence of pulmonary hypertension.

Angiocardiographic study (Fig. 3, *a–d*) consisted of selective aortography and of selective right ventriculography done through a catheter advanced from the thoracic aorta across the aortic valve and then into the right ventricle. Injection of contrast material into the right ventricle resulted in simultaneous opacification of both great vessels. The aorta opacified somewhat more densely than did the pulmonary trunk. In frontal view the pulmonary valve was slightly cephalad to the aortic valve. In addition, a "tongue-like," "filling defect" was present which appeared to divide the base of the right ventricle into two portions, a tract on the right leading to the aorta and one toward the left leading to the pulmonary trunk. Beneath this structure, which represented the parietal limb of the crista supraventricularis, lay a ventricular septal defect. In lateral view the anterior margin of the proximal ascending aorta overlapped the posterior margin of the proximal portion of the pulmonary trunk. In frontal view the selective aortogram showed the ascending aorta to be somewhat foreshortened and to exhibit less curvature than normal. In lateral view the ascending aorta did not appear unusual.

CASE IV. Female, aged 8 years.

Roentgenograms of the thorax (Fig. 1*d*) showed moderate cardiomegaly, right ventricular enlargement and prominence of the pulmonary trunk and of the central pulmonary vasculature.

Angiocardiograpnic study (Fig. 6, *a* and *b*) was done by advancing a catheter from the right atrium into the right ventricle and injecting contrast material into the latter chamber. This resulted in simultaneous and equal opacification of both great

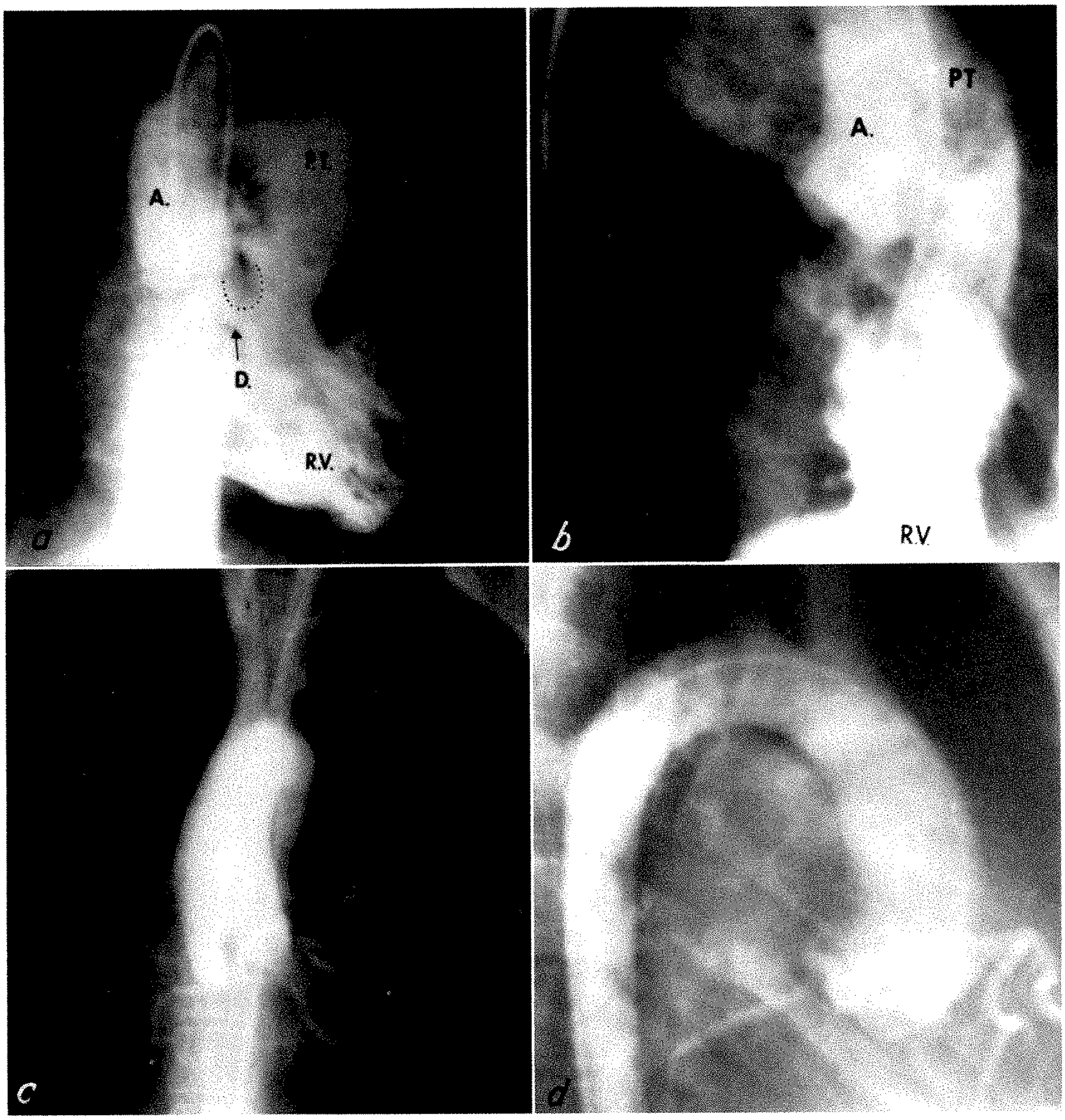


FIG. 3. Case III. Type I. (*a* and *b*) Selective right ventriculograms. Frontal and lateral views. A catheter was advanced from the femoral artery into the thoracic aorta, across the aortic valve and into the right ventricle (R.V.). Simultaneous opacification of both great vessels, with the aorta opacified somewhat more densely than the pulmonary trunk. Pulmonary trunk is larger than the aorta. Aortic and pulmonary valves lie nearly at the same level; the pulmonary valve is slightly more cephalad than the aortic valve. The ventricular septal defect (D.) is shown immediately beneath the "tongue-like" crista supraventricularis (dotted line) in *a*. The relationship of the aorta (A.) to the pulmonary trunk (P.T.) is shown in *b*. (*c* and *d*) Selective aortograms. Frontal and lateral views showing position and configuration of aorta.

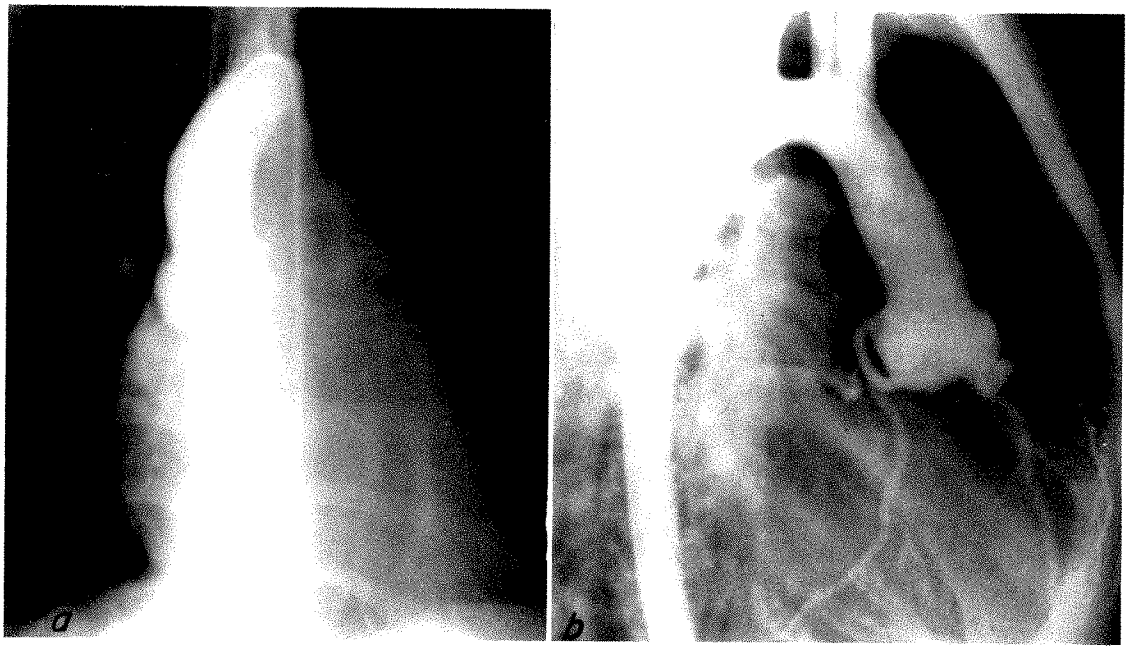


FIG. 4. Case II. Type I. (*a* and *b*) Selective aortograms. Frontal and lateral views showing position and configuration of aorta. The ascending aorta in lateral view is directed anteriorly throughout its entire course. The plane of the aortic valve is nearly horizontal.

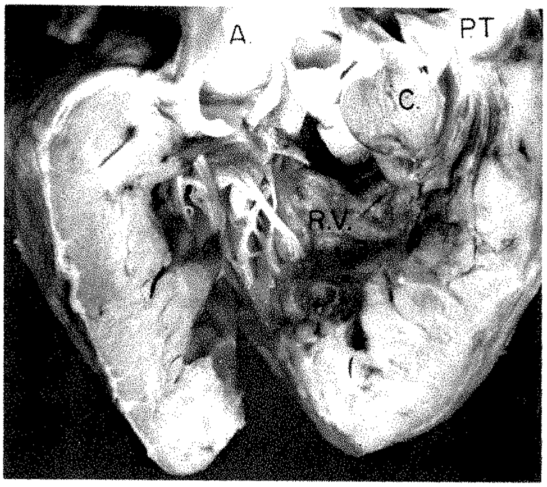


FIG. 5. Type I. Origin of both great vessels from the right ventricle. Sagittal section through origins of the aorta (A.) and pulmonary trunk (P.T.) revealing interior of right ventricle (R.V.). The prominent parietal limb of crista supraventricularis (C.) lies anterior to ventricular septal defect. The latter appears more closely allied to aortic origin than in other cases of classic Type I. Characteristically, the defect is remote from the pulmonary valve. Both semilunar valves lie at the same level. (Case 6 of Neufeld and associates.[6])

vessels. The pulmonary trunk was larger than the aorta. In frontal view, the parietal limb of the crista supraventricularis and the site of the ventricular septal defect were identifiable. The aortic and pulmonary valves lay in the same horizontal body plane. In lateral view, the aorta was superimposed over the posterior two-thirds of the pulmonary trunk.

CASE V. Male, aged 10 years.

Roentgenograms of the thorax (Fig. 1*b*) showed moderate cardiomegaly, right ventricular enlargement and striking prominence of the pulmonary trunk and of the central pulmonary vasculature.

Angiocardiographic study (Fig. 7, *a–c*) was accomplished by doing selective right ventriculography. After passing a catheter from the right atrium into the right ventricle and injecting contrast material, simultaneous and equal opacification of both great vessels was observed. The pulmonary trunk was larger than the aorta. In frontal view the site of the ventricular septal defect lying inferior to the crista supraventricularis was well defined. The pulmonary valve lay very slightly cephalad to the aortic valve. In lateral view the proximal segment of the aorta was superimposed over the posterior two-thirds of the proximal portion of the pulmonary trunk.

COMMENT

In each of the 5 cases with Type I malformation, the roentgenographic configuration of the heart and the appearances of the pulmonary trunk and of the pulmonary vasculature, respectively, were similar. This same combination of features may also be seen commonly in patients with ventricular septal defect associated with pulmonary hypertension.

Several anatomic features of Type I malformation were clearly demonstrated by angiocardiography. Both great vessels arose from the right ventricle and opacification of this chamber resulted in simultaneous opacification of these vessels. In the 4 cases in which right ventriculography was performed, the degree of opacification of the pulmonary trunk and aorta appeared equal in 2, the aorta was less densely opacified in 1 and the pulmonary trunk in the other.

In 4 cases, the relationship of the aorta to the pulmonary trunk was evaluated; in each, the proximal ascending aorta was superimposed over the proximal portion of the pulmonary trunk to a varying degree. In 1 case, the aorta completely overlay the pulmonary trunk, in 2 cases the aorta was superimposed over the posterior two-thirds of the pulmonary trunk and, in the remaining case, only the anterior portion of the proximal ascending aorta overlay the posterior aspect of the proximal pulmonary trunk.

The aortic and pulmonary valves were well defined in 3 cases. In these, the valves lay on the same horizontal body plane or the pulmonary valve lay very slightly cephalad to the aortic valve.

In lateral view, the ascending aorta was directed anteriorly throughout its entire course in 4 cases. In 1 case, the ascending aorta inclined posteriorly as it neared the valve. In frontal view in each case the as-

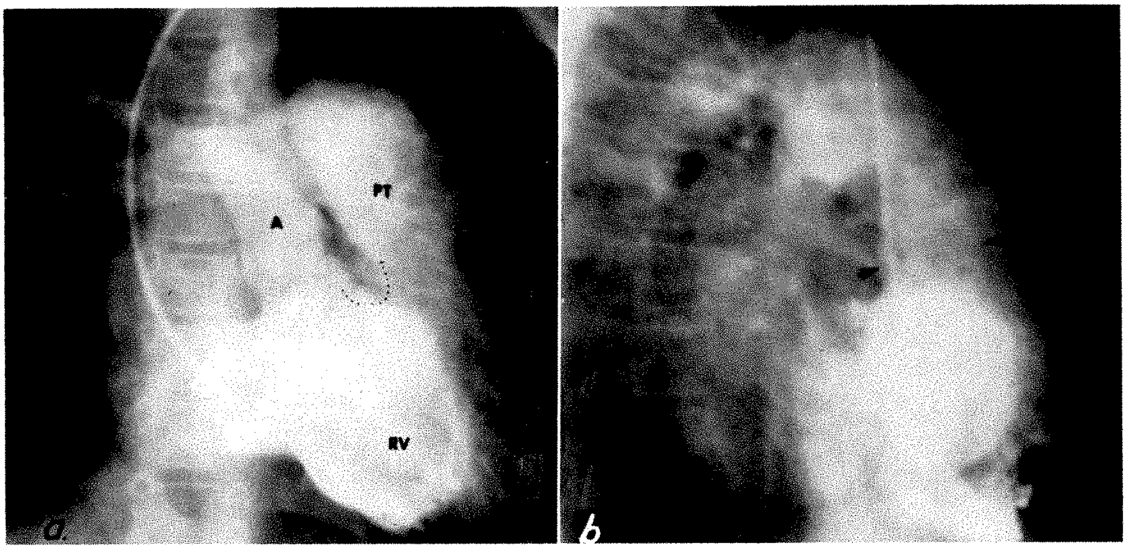


Fig. 6. Case IV. Type I. Selective right ventriculograms. (*a*) Frontal view. Contrast material injected into the right ventricle resulted in simultaneous and equal opacification of aorta and pulmonary trunk. The pulmonary trunk is larger than the aorta. The aortic and pulmonary valves lie on the same plane. Crista supraventricularis = dotted line. (*b*) Lateral view. The aorta (facing arrows) is superimposed on the posterior two-thirds of the pulmonary trunk.

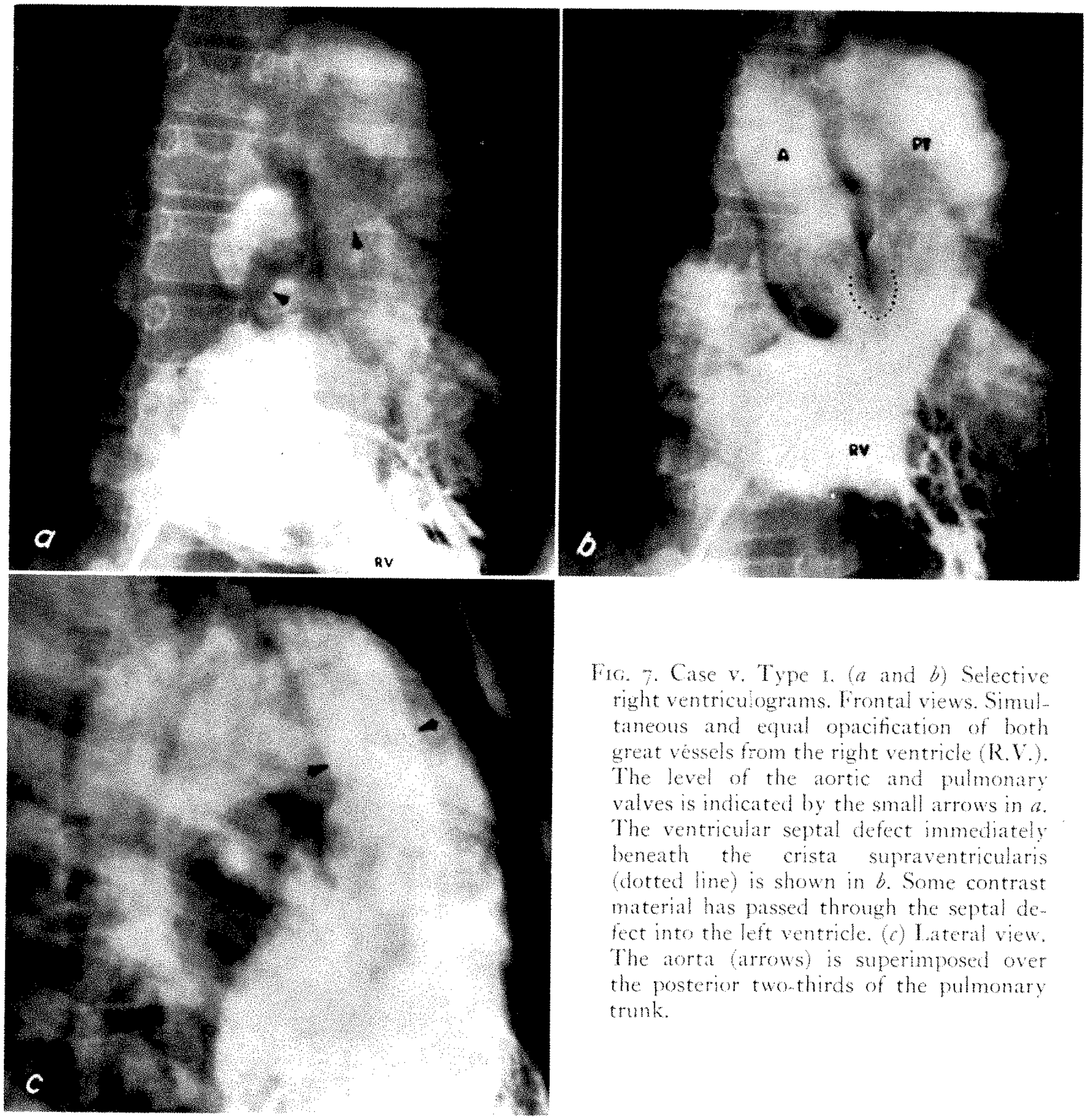


FIG. 7. Case V. Type I. (*a* and *b*) Selective right ventriculograms. Frontal views. Simultaneous and equal opacification of both great vessels from the right ventricle (R.V.). The level of the aortic and pulmonary valves is indicated by the small arrows in *a*. The ventricular septal defect immediately beneath the crista supraventricularis (dotted line) is shown in *b*. Some contrast material has passed through the septal defect into the left ventricle. (*c*) Lateral view. The aorta (arrows) is superimposed over the posterior two-thirds of the pulmonary trunk.

cending aorta appeared foreshortened and also appeared to exhibit less curvature than normal.

One additional important feature in right ventriculographic studies, in frontal view, was the almost invariable demonstration of the structures in the region of the crista supraventricularis. The parietal limb of the crista showed as a radiolucent "tongue" of varying size which clearly separated and defined the outflow tract of the right ventricle. The contrast material streamed from the right ventricle in a "V" fashion, one stream passing directly into the pulmonary trunk and the other stream passing through the ventricular septal defect to opacify the outflow tract of the left ventricle.

ATYPICAL TYPE I

ANATOMICALLY PROVED (3 CASES)

Roentgenologic Observations.

CASE VI. Male, aged 10 years.

Roentgenograms of the thorax (Fig. 1*f*) showed mild cardiomegaly and an elevated cardiac apex. The configuration was similar to the *coeur en sabot* noted in tetralogy of Fallot. The central pulmonary vasculature was slightly accentuated.

Angiocardiographic studies (Fig. 8, *a–d*) consisted of selective right ventriculography done through a catheter advanced from the right atrium and showed an enlarged, trabeculated right ventricle. There was dense opacification of the pulmonary trunk, but only a "wisp" of contrast material appeared in the aorta. The pulmonary

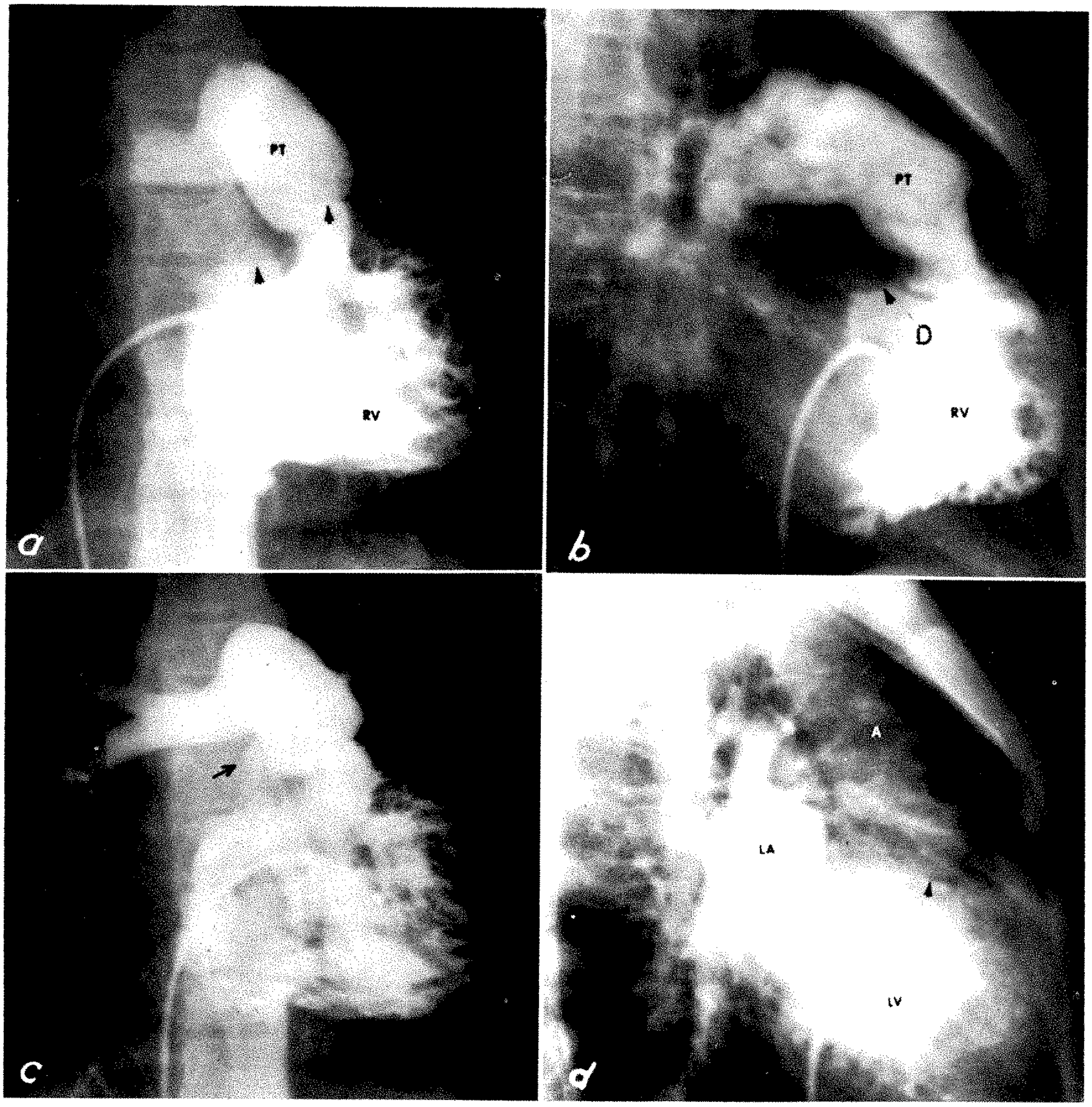


Fig. 8. Case vi. Atypical Type i. (*a*) Selective right ventriculogram. Frontal view. Opacification of the right ventricle (RV) and pulmonary trunk (PT). The pulmonary valve is clearly outlined (upper arrow). Contrast medium has passed through the ventricular septal defect and outlines the aortic valve (lower arrow). The pulmonary valve lies at a slightly higher level than the aortic valve. (*b*) Lateral view. The region of the ventricular septal defect (D) is seen to better advantage in this view. Arrow points to the aortic valve. (*c*) Frontal study made immediately following *a* and *b*. A small amount of contrast material may be seen entering the ascending aorta (arrow). (*d*) Film exposed later in the study. Lateral view. Contrast material outlining the left atrium (LA), left ventricle (LV) and aorta (A). The aorta fills mainly from the left ventricle. The site of the aortic valve is indicated by the arrow.

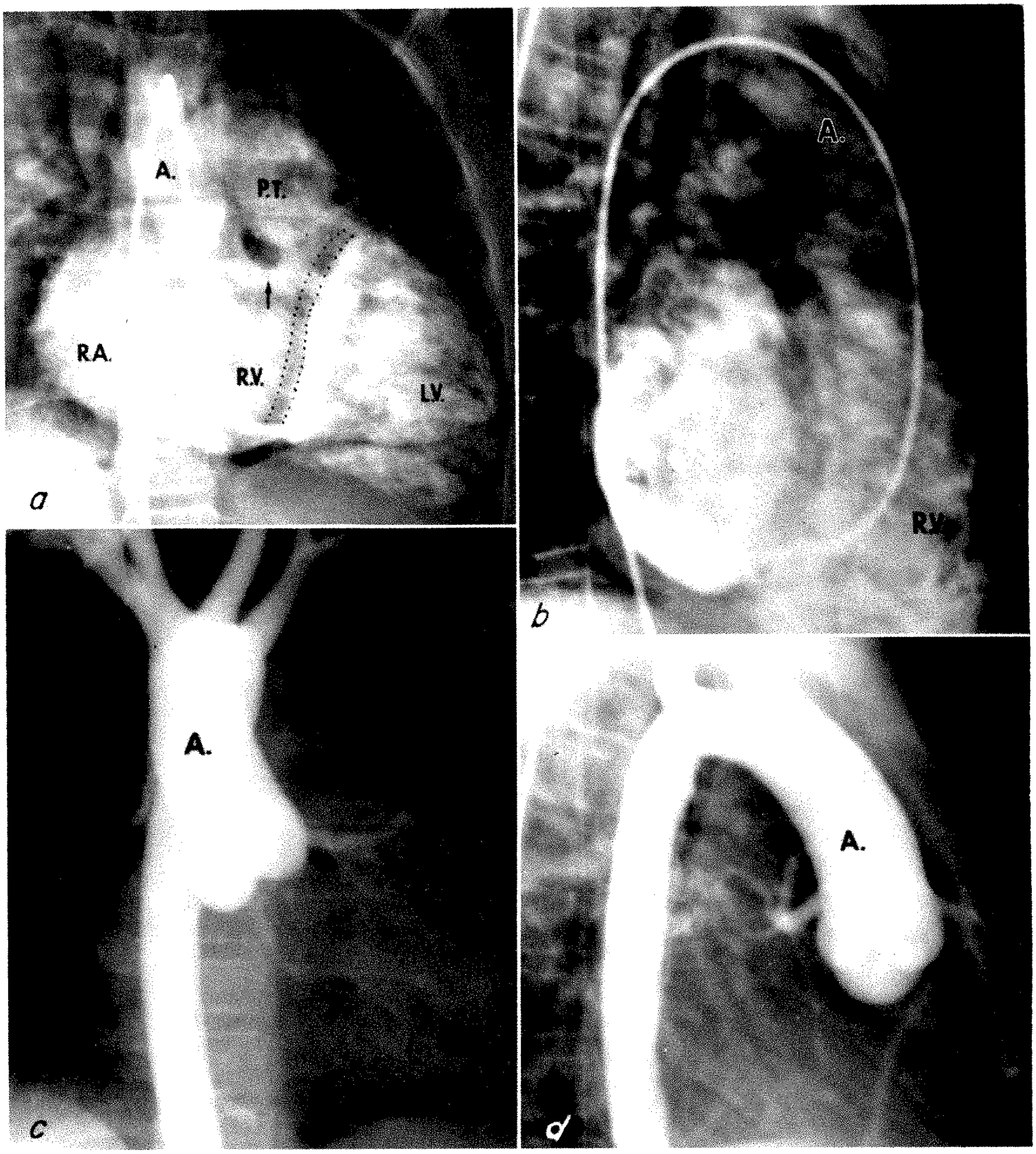


Fig. 9. Case VII. Atypical Type I. (*a*) Selective left ventriculogram. Frontal view. Injection of contrast material resulted in opacification of the left ventricle (L.V.), right ventricle (R.V.), right atrium (R.A.) and both great vessels. Right ventricle is enlarged. A band of decreased density extends obliquely upward and to the left from the base of the ventricle to the region of the pulmonary valve (dotted line). This "filling defect" represents a prominent parietal limb of the crista supraventricularis which is clearly shown in the necropsy specimen in Figure 11, *a* and *b*. The "tongue-like" septal limb of the crista supraventricularis (arrow) is well shown. The A-V commune defect lies immediately inferior to the crista. (*b*) Lateral view. (*c* and *d*) Selective aortograms showing the configuration and position of the thoracic aorta.

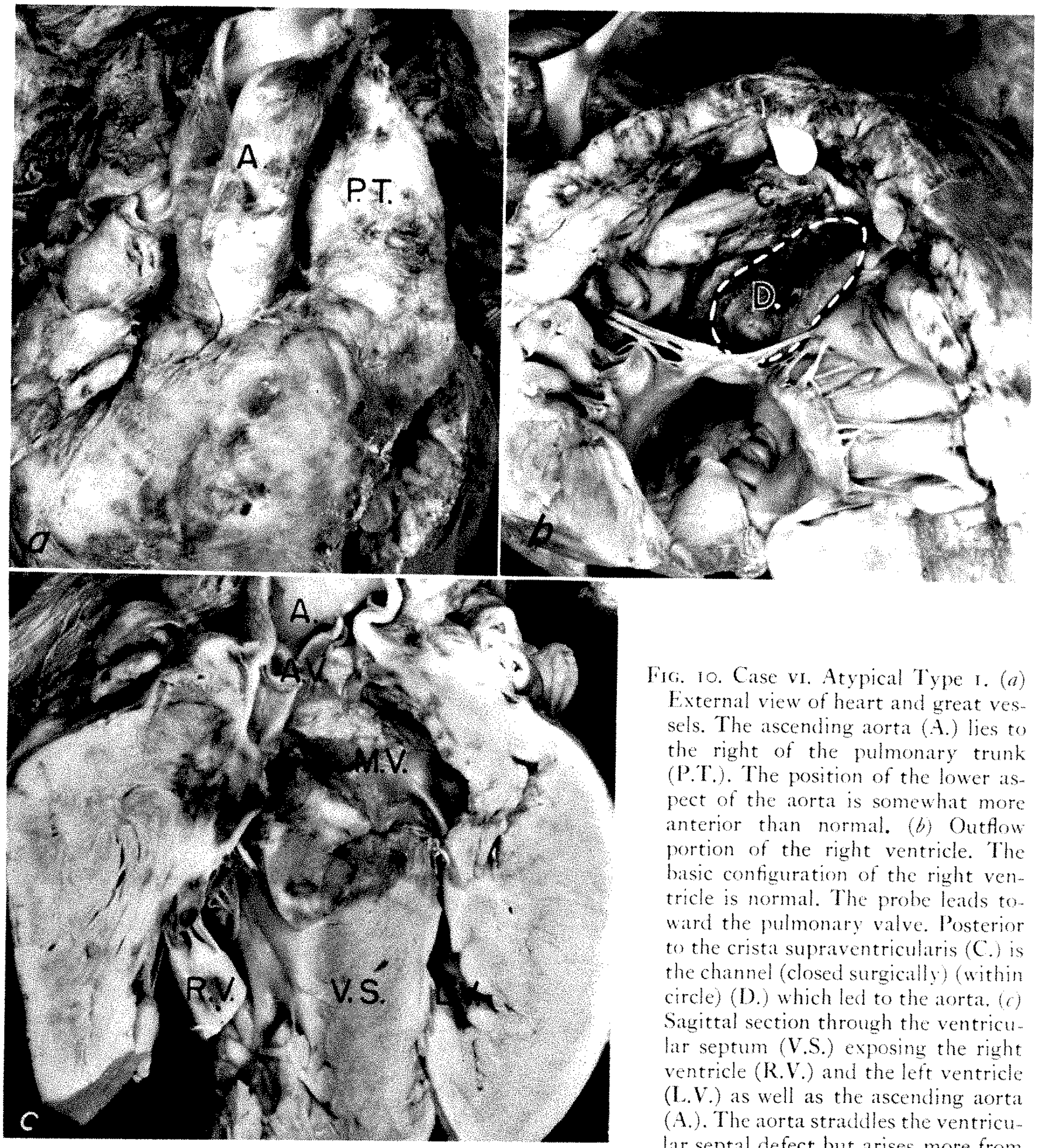


Fig. 10. Case vi. Atypical Type 1. (*a*) External view of heart and great vessels. The ascending aorta (A.) lies to the right of the pulmonary trunk (P.T.). The position of the lower aspect of the aorta is somewhat more anterior than normal. (*b*) Outflow portion of the right ventricle. The basic configuration of the right ventricle is normal. The probe leads toward the pulmonary valve. Posterior to the crista supraventricularis (C.) is the channel (closed surgically) (within circle) (D.) which led to the aorta. (*c*) Sagittal section through the ventricular septum (V.S.) exposing the right ventricle (R.V.) and the left ventricle (L.V.) as well as the ascending aorta (A.). The aorta straddles the ventricular septal defect but arises more from the right ventricle than the left. There is continuity between the aortic valve (A.V.) and the anterior leaflet of the mitral valve (M.V.).

valve lay at a higher level than the aortic valve. No "tongue-like" crista separating the two outflow tracts was visible.

Case vii. Female, aged 9 years.

Roentgenograms of the thorax (Fig. 1*e*) showed marked cardiomegaly with biventricular and bi-atrial enlargement. The pulmonary trunk and central pulmonary vasculature were enlarged.

Angiocardiographic studies (Fig. 9, *a–d*) consisted of advancing a catheter across the aortic valve and into the left ventricle. Injection of contrast material resulted in opacification of both ventricles, the right atrium and both great vessels. In frontal view, a very prominent "tongue-like" crista separated the outflow tracts leading to the aorta and the pulmonary trunk. The aortic and pulmonary valves lay at the same level. In lateral view, the ascending aorta was far anterior and lay immediately substernal.

Case viii. Male, aged 16 years.

Roentgenograms of the thorax (Fig. 1*g*) showed fairly marked cardiomegaly with enlargement of the pulmonary trunk and central pulmonary vasculature. A soft tissue density in the left superior mediastinum represented a left superior vena cava.

Pathologic Observations.

In each of the above 3 cases, the ventricular septal defect lay below the crista supraventricularis (Fig. 10, *a–c;* 11, *a–c;* and 12). This finding was in common with the classic examples of Type I. The atypical feature was that in each of these cases there was continuity between the aortic and mitral valves. While the features mentioned are duplicated in the usual type of ventricular septal defect, the aortic orifice was positioned directly over the right ventricle rather than straddling the ventricular septal defect. As the aortic origin was not over the left ventricle, the anterior mitral leaflet was long as it maintained continuity with the malpositioned aorta. Another atypical feature was that in Cases vi and viii the aortic valve lay somewhat lower than the pulmonary valve. In Case vii the two semilunar valves lay at about the same level. This case also showed, among the intracardiac malformations, a persistent common atrioventricular canal and communication of a persistent left superior vena cava with the left atrium. The relatively high position of the aortic valve may have been more closely related to the association of persistent common atrioventricular canal than to the fact that the aortic origin overlay the right ventricle.

It is of interest that in each of the 3 cases in this group the crista supraventricularis, particularly its parietal band, was hypertrophied anatomically. In Case vii it was responsible for the "tongue-like" mass which separated the subpulmonary from the subaortic areas of the right ventricle. In Case vi the crista was not demonstrated angiocardiographically and in Case viii, no angiocardiographic studies had been done which could have tested whether such a process would have been evident in contrast studies.

In Case viii, an associated malformation took the form of atresia of the right superior vena cava, while the left superior vena cava was patent and joined the coronary sinus (case reported by Karnegis and associates[4]).

COMMENT

Roentgenologically and angiocardiographically, Case vi was the most atypical in this group. The configuration of the heart was unusual, the pulmonary and aortic valves lay at different levels and no definite crista was visible in the frontal view. In addition, there was practically no opacification of the aorta from the right ventricle.

CLASSIC TYPE IIA
(TAUSSIG-BING COMPLEX)

ANATOMICALLY PROVED (2 CASES)

Roentgenologic Observations.

Case ix. Male, aged 1 year. (Case 8 of Neufeld and associates[6].)

Roentgenograms of the thorax (Fig. 13*c*) showed fairly marked cardiomegaly, right ventricular and left atrial enlargement and enlargement of the pulmonary trunk and central pulmonary vasculature.

Angiocardiographic studies (Fig. 14, *a* and *b*) consisted of selective right ventriculography done through a catheter passed from the right atrium. Injection of contrast material resulted in simultaneous opacification of both great vessels. The aorta opacified more densely than the pulmonary trunk. A definite "tongue-like"

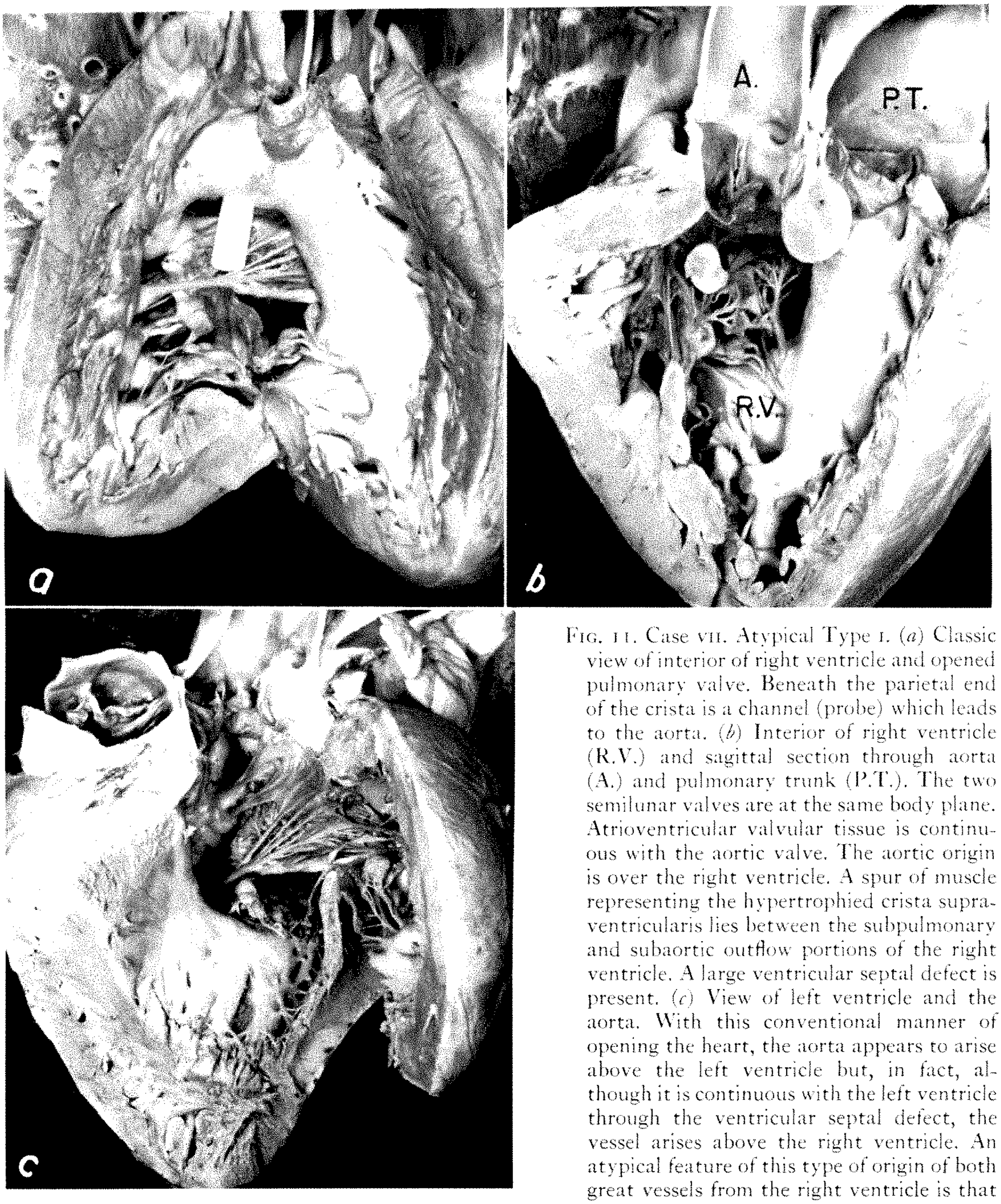


Fig. 11. Case vii. Atypical Type i. (*a*) Classic view of interior of right ventricle and opened pulmonary valve. Beneath the parietal end of the crista is a channel (probe) which leads to the aorta. (*b*) Interior of right ventricle (R.V.) and sagittal section through aorta (A.) and pulmonary trunk (P.T.). The two semilunar valves are at the same body plane. Atrioventricular valvular tissue is continuous with the aortic valve. The aortic origin is over the right ventricle. A spur of muscle representing the hypertrophied crista supraventricularis lies between the subpulmonary and subaortic outflow portions of the right ventricle. A large ventricular septal defect is present. (*c*) View of left ventricle and the aorta. With this conventional manner of opening the heart, the aorta appears to arise above the left ventricle but, in fact, although it is continuous with the left ventricle through the ventricular septal defect, the vessel arises above the right ventricle. An atypical feature of this type of origin of both great vessels from the right ventricle is that the mitral valve is continuous with the aorta. This heart shows the features of persistent common atrioventricular canal, in addition to those of atypical origin of both great vessels from the right ventricle.

filling defect at the base of the right ventricle formed an outflow tract to the aorta and another to the pulmonary trunk. The outflow tract leading to the aorta appeared narrowed. The pulmonary and aortic valves lay at the same level.

In lateral view the ascending aorta was directed anteriorly throughout its entire course and was superimposed over the posterior one-half of the proximal portion of the pulmonary trunk. Coarctation of the aorta was present and there was mild hypo-

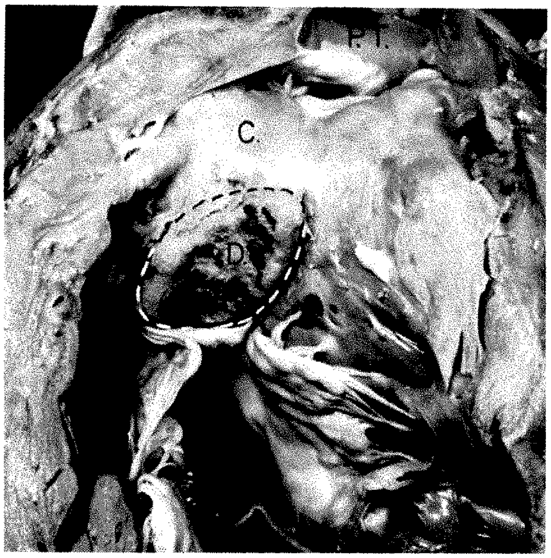


Fig. 12. Case viii. Atypical Type i. Outflow portion of the right ventricle. The pulmonary trunk (P.T.) is in a normal position. The channel leading to the aorta (D. in dotted circle) represents the surgical obliteration of the communication between the aorta and the right ventricle. This channel lies postero-inferior to the crista supraventricularis (C.). In this instance there was continuity between the aortic and mitral valves.

plasia of the aorta extending between the left common carotid and left subclavian arteries.

Case x. Male, aged 4 months.

Roentgenograms of the thorax (Fig. 13, *a* and *b*) showed fairly marked cardiomegaly, and right ventricular and left atrial enlargement. The pulmonary trunk and central pulmonary vasculature were prominent.

Angiocardiographic studies (Fig. 15, *a–f*) consisted, initially, of a forward angiocardiogram which showed sequential opacification of the right atrium, right ventricle and a transposed aorta. In addition, there was minimal opacification of an enlarged pulmonary trunk. A definite "tongue-like" muscle spur separated the two outflow tracts. In lateral view, the aorta was superimposed over the posterior two-thirds of the pulmonary trunk. Selective left ventriculography was done through a catheter advanced from the right atrium, right ventricle and then through the septal defect into the left ventricle. Contrast material injected into the left ventricle resulted in immediate opacification of the pulmonary trunk. A small amount of contrast material outlined the outflow tract leading into the aorta, but none appeared in the aorta itself. Subsequent roentgenograms in the same study showed opacification of the left atrium, left ventricle and pulmonary trunk.

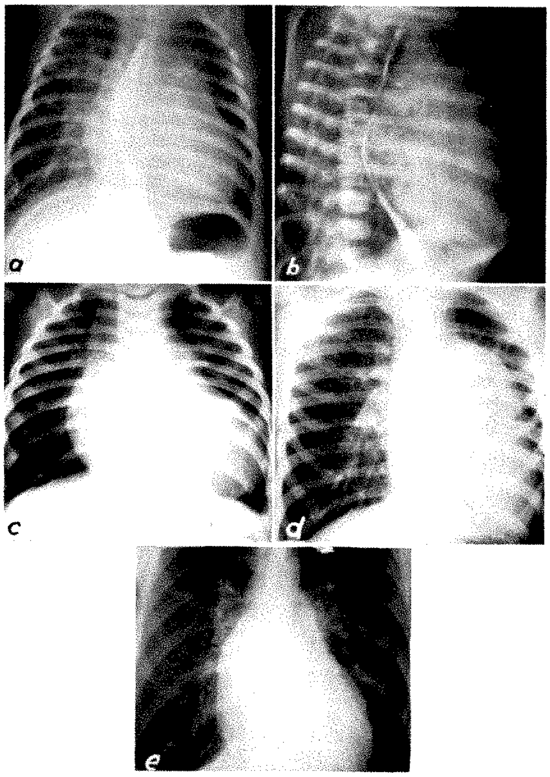


Fig. 13. (*a–d*) Roentgenograms of the thorax in 3 cases of origin of both great vessels from the right ventricle, Type ii, showing moderate to marked cardiomegaly and striking prominence of the pulmonary trunk and central pulmonary vasculature. (*a* and *b*) Case x, male, 4 months. The frontal and lateral views show left atrial enlargement, a common finding in this group of cases. (*c*) Case ix, male, 1 year. (*d*) Case xi, female, 4½ years. (*e*) Case xiv, male, 25 years. Frontal roentgenogram in unusual type of origin of both great vessels from the right ventricle showing cardiomegaly, enlargement of the pulmonary trunk and central pulmonary vasculature. Convex prominence of the upper portion of the right cardiac border (arrow) represents wall of the infundibular chamber from which the aorta arose.

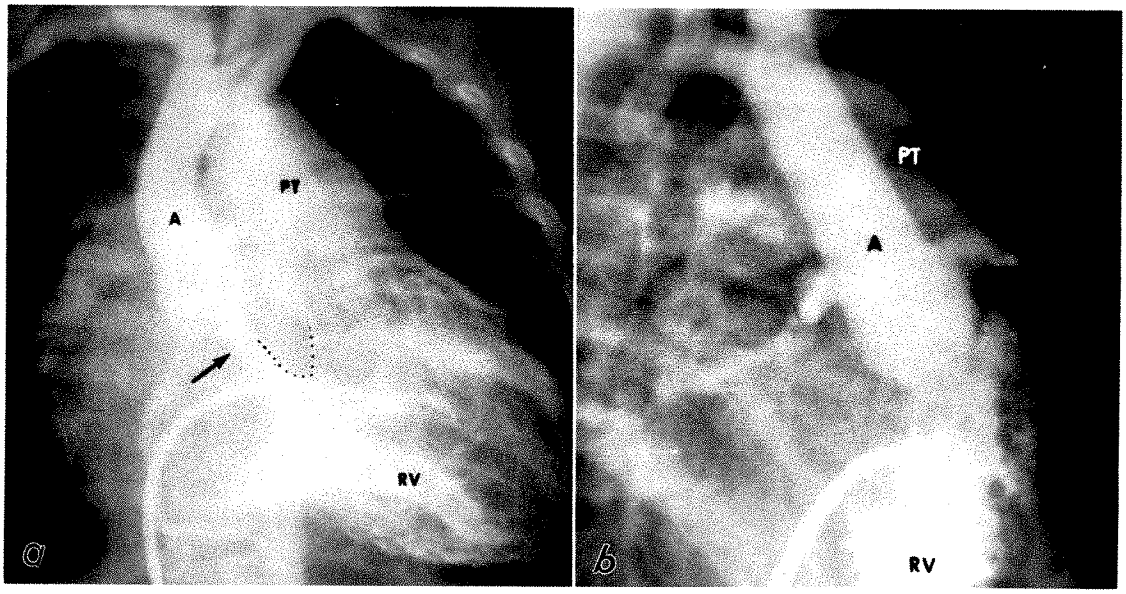


FIG. 14. Case IX. Type IIA. (*a* and *b*) Selective right ventriculograms. Frontal and lateral views show simultaneous opacification of both great vessels from the right ventricle (RV). The aorta (A) is more densely opacified than the pulmonary trunk (PT). The spur of muscle (dotted line) dividing the base of the right ventricle into an outflow tract for each great vessel is shown in frontal view. The narrowed outflow tract leading to the aorta is indicated by the arrow. In lateral view, the ascending aorta is directed anteriorly throughout its entire course.

Pathologic Observations.

Each specimen exhibited the classic features of Type IIA origin of both great vessels from the right ventricle (Fig. 16, *a* and *b*).

The pulmonary trunk was obviously wider than the aorta. From the exterior, the position of the two great vessels was not remarkable. Within the heart, the aorta arose from the right ventricle to the right of the origin of the pulmonary trunk.

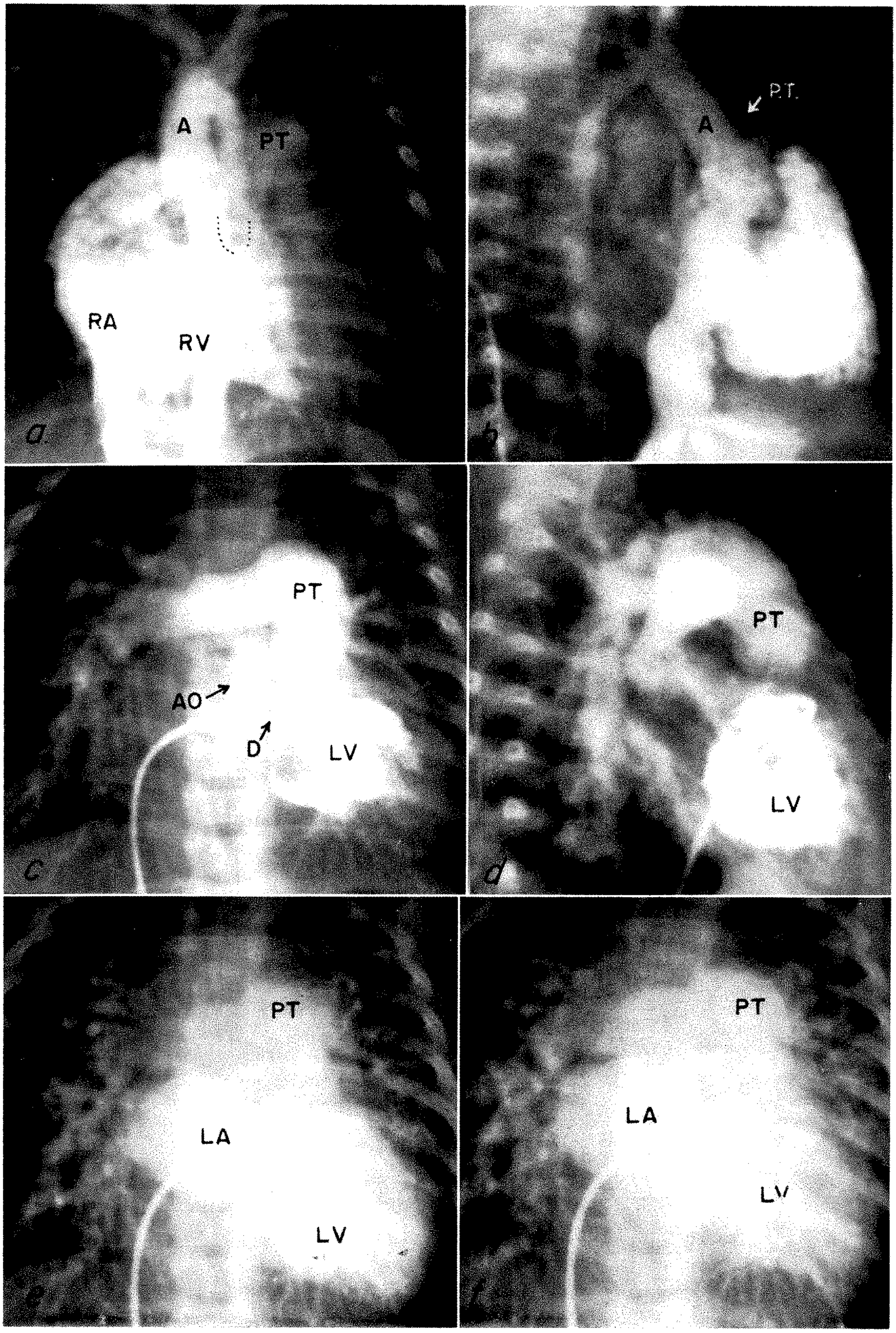
The parietal limb of the crista was prominent and was divided into two portions, an anterior and a posterior. Between these two segments was the channel leading to the aorta. In the vicinity of the ventricular septum, the anterior division of the parietal limb of the crista constituted a stout mass of muscle which subdivided the subpulmonary region of the right ventricular base from the subaortic region. This mass is considered to represent the "tongue-like" spur observed in ventriculograms.

In each case, the ventricular septal defect was large and lay immediately under the left aspect of the pulmonary valve and above the septal limb of the crista supraventricularis.

COMMENT

The roentgenographic and angiocardiographic findings in these 2 patients were similar. Roentgenograms of the thorax showed cardiomegaly, right ventricular and left atrial enlargement, striking prominence of the pulmonary trunk and a moderate to marked increase in the pulmonary vasculature. Selective angiocardiograms in frontal view showed a definite "tongue-like" spur of muscle separating the ventricular outflow tracts. The appearance of the spur was not obviously different from that seen in Type I origin of both great vessels from the right ventricle.

Both cases of Type IIA showed simultaneous opacification of both great vessels from the right ventricle, the aorta opacifying more densely than the pulmonary trunk.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b
PT
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c
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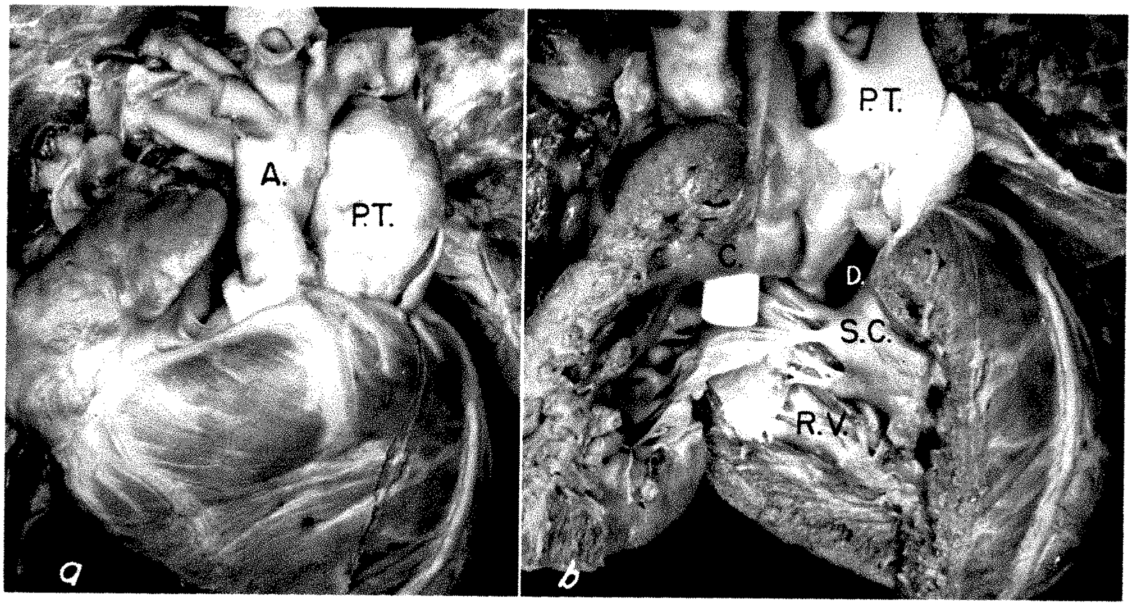

Fig. 16. Case x. Type IIA. Origin of both great vessels from right ventricle. (*a*) External view of heart and great vessels. The ascending aorta (A.) and the pulmonary trunk (P.T.) are parallel. The lower aspect of the ascending aorta is somewhat more anterior than normal. (*b*) Interior of right ventricle (R.V.) and pulmonary trunk (P.T.). The ventricular septal defect (D.) lies immediately beneath the pulmonary valve and above the septal limb of the crista supraventricularis (S.C.). The probe lies within a bifid parietal limb of the crista supraventricularis and leads to the aortic valve. The upper half of the bifid crista supraventricularis (C.) is prominent and represents the dividing ridge between the subaortic and subpulmonary regions of the right ventricle.

The aortic and pulmonary valves lay at the same level. In lateral view the ascending aorta was directed anteriorly throughout its entire length, and it was superimposed over the posterior aspect of the pulmonary trunk. The angiocardiographic studies in each case supported the concept of the usual hemodynamics in this type of malformation; *i.e.*, the primary flow from the right ventricle is into the aorta and the primary flow from the left ventricle is into the pulmonary trunk.

TYPE IIB

ANATOMICALLY PROVED (1 CASE)

Roentgenologic Observations.

Case xi. Female, aged 4½ years. (Case 10 of Neufeld and associates.[6])

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Fig. 15. Case x. Type IIA. (*a* and *b*) Forward angiocardiograms. Frontal and lateral views. Sequential opacification of the inferior vena cava, right atrium (RA), right ventricle (RV) and both great vessels. The major portion of the contrast material flows into the aorta (A) and there is only minimal opacification of the enlarged pulmonary trunk (P.T.). Muscle spur (dotted line) separates outflow tracts in frontal view. In lateral view the ascending aorta is directed anteriorly throughout its entire course. Arrow points to anterior margin of pulmonary trunk. (*c* and *d*) Selective left ventriculograms. The catheter was advanced from the right atrium into the right ventricle and across the septal defect into the left ventricle. Opacification of the left ventricle (LV) and an enlarged pulmonary trunk (PT). A small amount of contrast material enters the aortic outflow tract (AO) through the ventricular septal defect (D). (*e* and *f*) Later ventriculograms in the same study as *c* and *d*. (*e*) Frontal view. Contrast material has just reached the left atrium (LA) and left ventricle (LV). There is still faint opacification of the pulmonary trunk (PT). (*f*) Subsequent frontal view showing reopacification of the pulmonary trunk, which indicates that the flow from the left ventricle is primarily into the pulmonary trunk. The above series of films demonstrates the hemodynamic events in this type of malformation; blood flow from the right ventricle is primarily into the aorta and flow from the left ventricle is primarily into the pulmonary trunk.

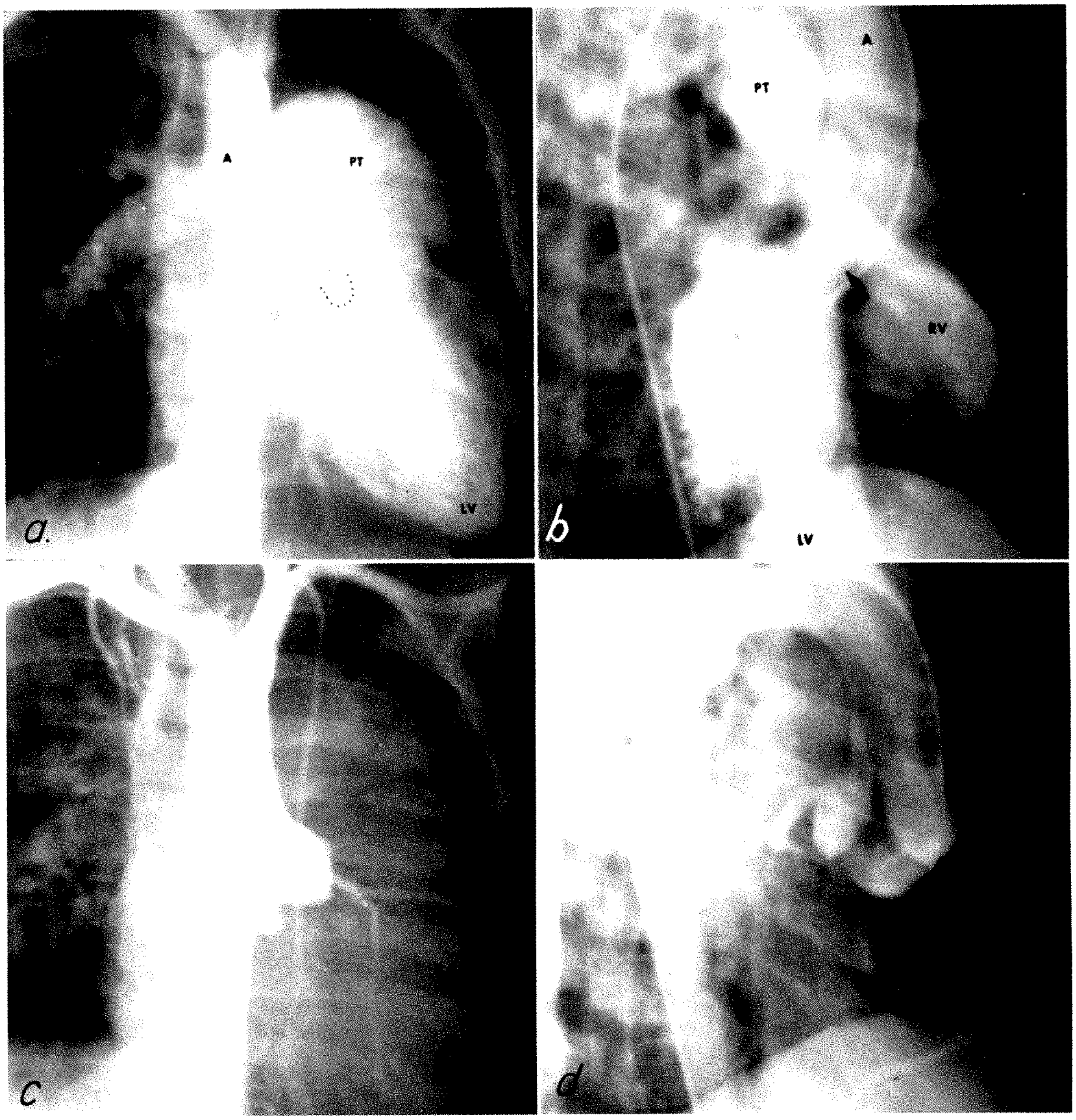

FIG. 17. Case XI. Type IIB. (*a* and *b*) Selective left ventriculograms. (*a*) Frontal view. Opacification of left ventricle (LV) and simultaneous and equal opacification of both great vessels. Small muscle spur (dotted line) separates the right ventricular outflow tracts. The ventricular septal defect lies immediately beneath the spur. (*b*) Lateral view. The site of the ventricular septal defect is evident (arrow). Contrast material may be seen passing from the left ventricle (LV) across the septal defect and into the right ventricle (RV). The relationship of the aorta (A) to the pulmonary trunk (PT) is shown. (*c* and *d*) Selective aortograms. Frontal and lateral views showing the position and configuration of the aorta. Coarctation of the aorta is also demonstrated.

Roentgenograms of the thorax (Fig. 13*d*) showed fairly marked cardiomegaly, right ventricular enlargement, enlargement of the pulmonary trunk and prominent central pulmonary vasculature.

Angiocardiographic studies (Fig. 17, *a–d*) consisted of selective left ventriculography performed by passing a catheter from the aorta across the aortic valve into the left ventricle. Injection of contrast material resulted in equal intensity of opacification of both great vessels. The pulmonary and

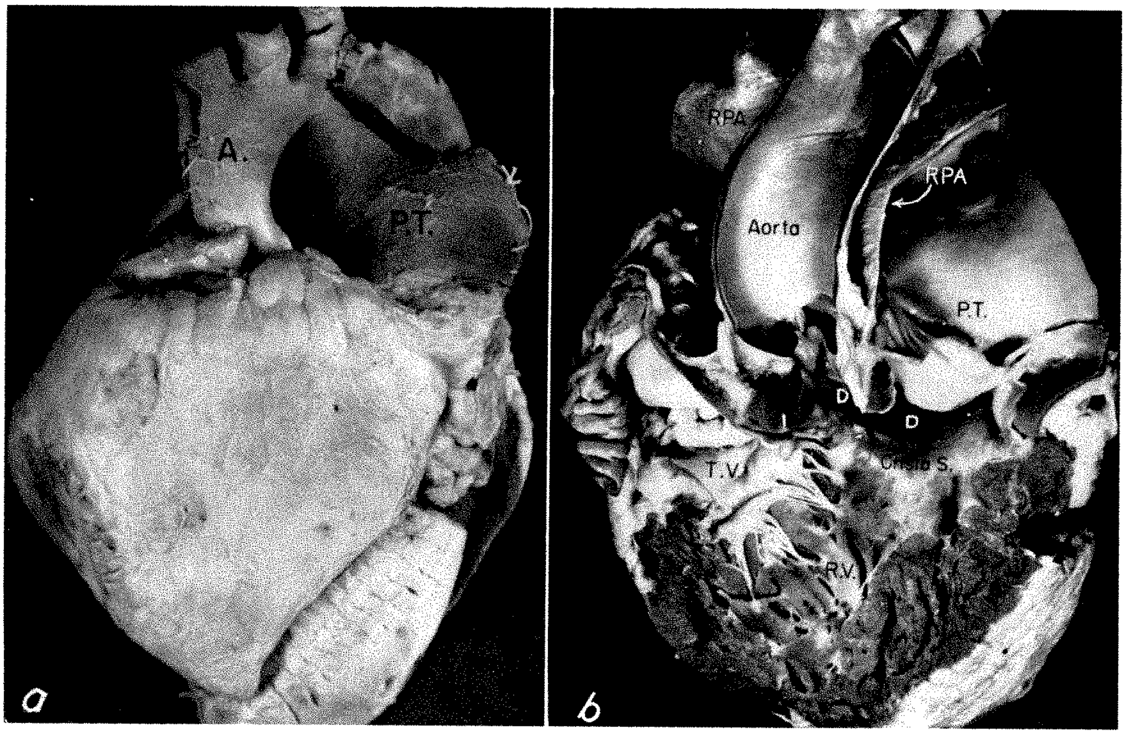

Fig. 18. Case xi. Type iib. Origin of both great vessels from right ventricle. (*a*) External view of heart and great vessels viewed from in front and slightly from the right. The ascending aorta (A.) lies to the right of the pulmonary trunk (P.T.), which is dilated. (*b*) Sagittal section through the great vessels and interior view of the right ventricle (R.V.) and a portion of tricuspid valve (T.V.). The ventricular septal defect (D.) lies beneath the pulmonary valve and slightly beneath the aortic valve. A spur of tissue separates the base of the right ventricle in the intravalvular position. The septal limb of the crista supraventricularis (Crista S.) lies beneath the ventricular septal defect. The pulmonary trunk (P.T.) is dilated. RPA = right pulmonary artery. (From Neufeld and associates.[6])

aortic valves lay at the same level. A small muscular spur separated the ventricular outflow tracts. In lateral view, the aorta lay almost entirely anterior to the pulmonary trunk. Coarctation of the aorta was also present.

Pathologic Observations.

The pathologic findings in this case have previously been described in the report of Neufeld and associates[6] (Case 10). In essence, this example of origin of both great vessels from the right ventricle was characterized by a large ventricular defect lying above the septal limb of the crista supraventricularis. The defect, which primarily lay under the pulmonary valve, also extended beneath the aortic valve. The latter feature induced separation of this case as representing Type iib (Fig. 18, *a* and *b*), while those cases in which the ventricular septal defect did not extend under the aortic valve were designated as Type iia.

A relatively thin spur of muscle, the parietal limb of the crista, separated the subpulmonary from the subaortic regions of the right ventricle.

COMMENT

In this patient, the appearance in conventional roentgenograms of the thorax was similar to that seen in patients classified as Type iia. The angiocardiographic appearance, however, was different in that the aorta was more transposed than in Type iia. Only a small muscular spur was present, and the defect extended beneath the aortic valve. This anatomic situation also allowed equal opacification of both great vessels, a feature not observed in Type IIA.

ANATOMIC ENTITIES HAVING ANGIOCARDIOGRAPHIC FINDINGS IN COMMON WITH TYPE II

The cases included in this group illustrate the fact that certain other anatomic entities may resemble the angiocardiographic findings in anatomically classic examples of Type II origin of both great vessels from the right ventricle, since the fundamentals of blood flow may be similar.

RIGHT VENTRICULAR AORTA AND BIVENTRICULAR PULMONARY TRUNK

Roentgenologic Observations.

Case XII. Male, aged 10 weeks.

Roentgenograms of the thorax (Fig. 19, *a* and *b*) showed marked cardiomegaly, right atrial, right ventricular and left atrial enlargement. In addition, there was a striking prominence of the pulmonary vasculature.

Angiocardiographic studies (Fig. 19, *c* and *d*) consisted of inserting a catheter into the right brachial artery and advancing it into the aorta, across the aortic valve and into a ventricular chamber. Contrast material was injected and resulted in opacification of the right ventricle and simultaneous opacification of both great vessels, the aorta more densely than the pulmonary trunk. In frontal view, a spur of muscle divided the basal portion of the right ventricle into two outflow tracts, one leading to the aorta on the right, and the other leading to the pulmonary trunk on the left. The "V" shaped flow of contrast material from the right ventricle into the respective outflow tracts appeared much the same as was seen in Type IIA. The great vessels showed a side-by-side relationship. In lateral view, the ascending aorta was directed anteriorly throughout its entire length and was superimposed over the posterior two-thirds of the proximal portion of the pulmonary trunk. Coarctation of the aorta in a classic location and tubular hypoplasia of the aortic arch, extending between the left common carotid and left subclavian artery, were also demonstrated.

Pathologic Observations.

Pathologically, this case, previously reported by Elliott and associates[3] (Case 2), exhibited an unusual form of transposition (Fig. 20, *a* and *b*). From external examination, the positions of the great vessels were not abnormal. Within the heart, it was evident that the aorta arose from the right ventricle and to the right of the pulmonary trunk. The pulmonary trunk, which straddled a ventricular septal defect, arose more over the left ventricle than over the right. The pulmonary valve made continuity with the mitral valve. A prominent parietal limb of the crista separated the base of the right ventricle into subpulmonary and subaortic areas.

The fact that part of the pulmonary origin was from the left ventricle precludes an anatomic diagnosis of classic Type II origin of both great vessels from the right ventricle. The condition has some resemblance to complete transposition, but the fact that part of the pulmonary origin is from the right ventricle is the basis for excluding that anatomic diagnosis.

COMPLETE TRANSPOSITION OF GREAT VESSELS

Roentgenologic Observations.

Case XIII. Female, aged 2½ months.

Roentgenograms of the thorax showed no distinguishing features.

Forward angiocardiographic studies (Fig. 21, *a* and *b*) revealed sequential opacification of the enlarged right atrium and right ventricle, followed by simultaneous opacification of both great vessels which showed a "side-to-side" relationship in frontal view. The aorta became densely opacified and the pulmonary trunk to a lesser degree. Except for absence of an obvious "tongue-like" spur below the origins of the great vessels, the findings could not be distinguished from those of Type II origin of both great vessels from the right ventricle.

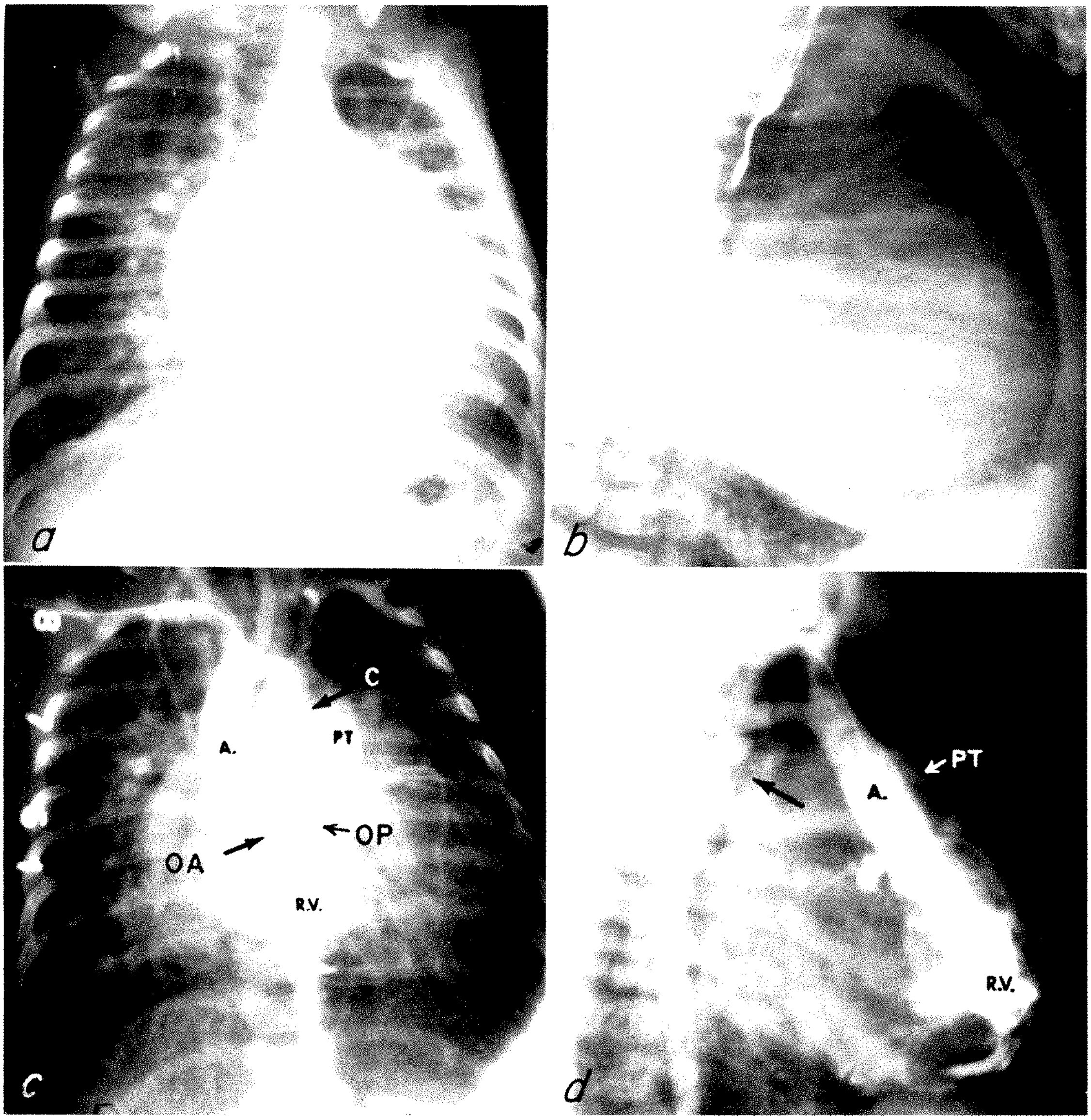

Fig. 19. Case xii. Right ventricular aorta and biventricular pulmonary trunk. (*a* and *b*) Frontal and lateral roentgenograms of the thorax showing marked cardiomegaly and increased pulmonary vasculature. (*c* and *d*) Selective right ventriculograms in frontal and lateral views. Catheter was advanced from the aorta (A.) across the aortic valve and into the right ventricle (R.V.). Injection of contrast material into the right ventricle resulted in simultaneous opacification of both great vessels. The aorta opacified more densely than the pulmonary trunk (PT). The pulmonary trunk is larger than the aorta. In frontal view, a muscular spur is seen dividing the base of the right ventricle into a subaortic outflow tract (OA) and an outflow tract to the pulmonary trunk (OP). Coarctation of the aorta (C) is also shown. In addition, in lateral view, there is a segment of hypoplasia of the aortic arch extending from the left common carotid artery to the left subclavian artery. The ascending aorta is directed anteriorly throughout its entire course and is superimposed on the pulmonary trunk. Arrow points to anterior margin of pulmonary trunk. The aortic and pulmonary valves are at the same level.

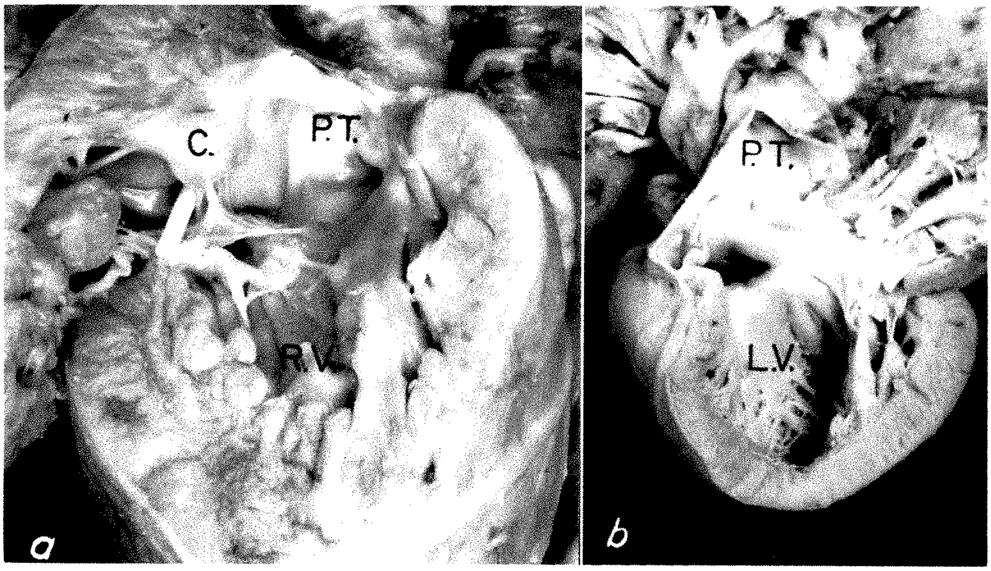

Fig. 20. Case xii. Right ventricular aorta and biventricular pulmonary trunk. (Courtesy of Elliott and associates and *Am. Heart J.*[3]) (*a*) Interior of right ventricle (R.V.). The pulmonary trunk (P.T.) arises partially from the right ventricle above a ventricular septal defect. The probe leads to the aortic origin which is separated from the pulmonary origin by a prominent parietal limb of the crista supraventricularis (C.). (*b*) Interior of left ventricle and opened pulmonary trunk (P.T.). The pulmonary trunk arises mainly from the left ventricle.

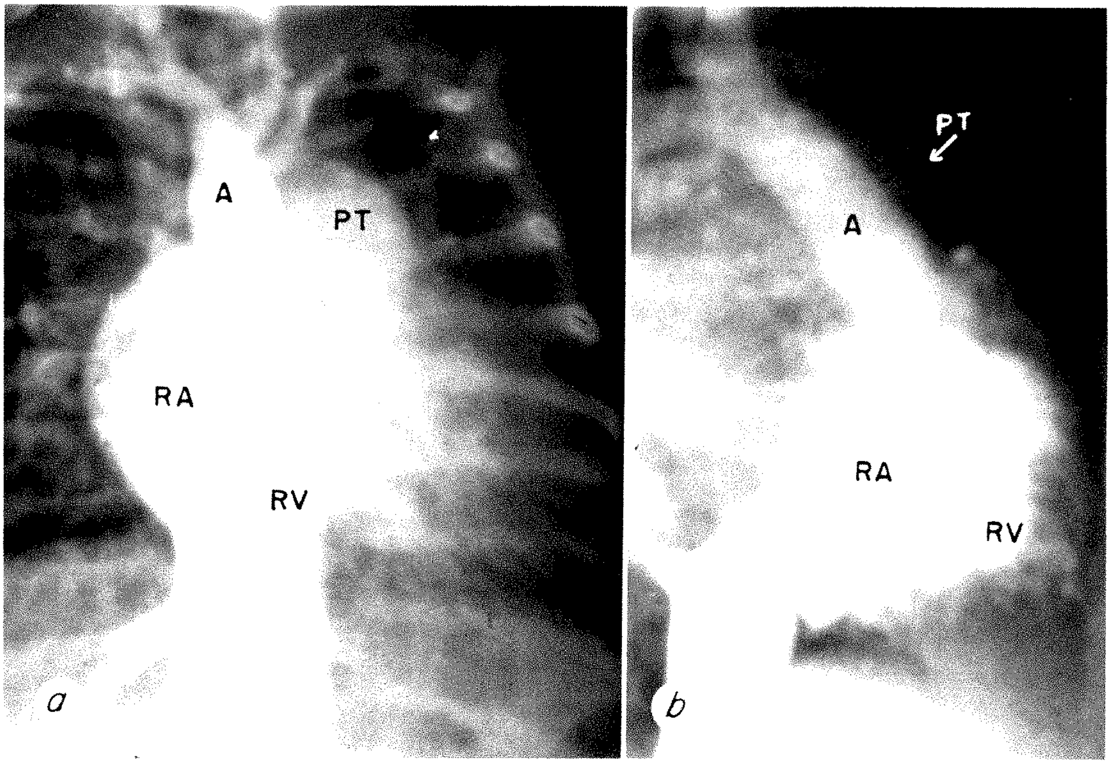

Fig. 21. Case xiii. Complete transposition of great vessels. (*a* and *b*) Forward angiocardiograms in frontal and lateral views showing simultaneous opacification of both great vessels from the right ventricle. The aorta (A) opacifies more densely than the pulmonary trunk (PT). The side-to-side relationship of the

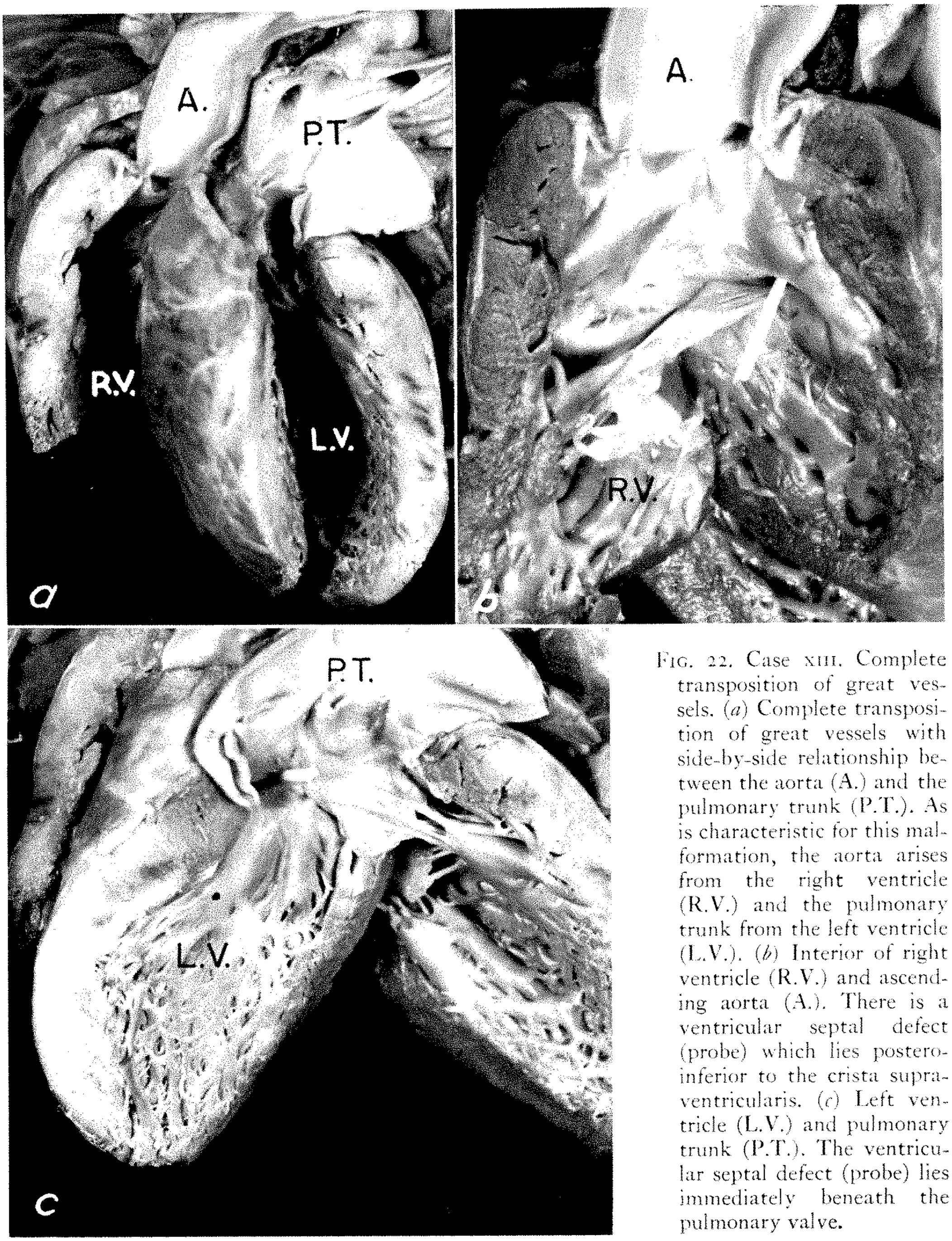

Fig. 22. Case xiii. Complete transposition of great vessels. (*a*) Complete transposition of great vessels with side-by-side relationship between the aorta (A.) and the pulmonary trunk (P.T.). As is characteristic for this malformation, the aorta arises from the right ventricle (R.V.) and the pulmonary trunk from the left ventricle (L.V.). (*b*) Interior of right ventricle (R.V.) and ascending aorta (A.). There is a ventricular septal defect (probe) which lies postero-inferior to the crista supraventricularis. (*c*) Left ventricle (L.V.) and pulmonary trunk (P.T.). The ventricular septal defect (probe) lies immediately beneath the pulmonary valve.

Pathologic Observations.

Pathologically, the specimen exhibited classic features of complete transposition of the great vessels with a ventricular septal defect and with a "side-to-side" relationship between the great vessels[1,2] (Fig. 22, *a–c*).

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great vessels is shown in *a*. In *b* is shown the transposed aorta which is superimposed upon the enlarged pulmonary trunk. RA = right atrium; RV = right ventricle.

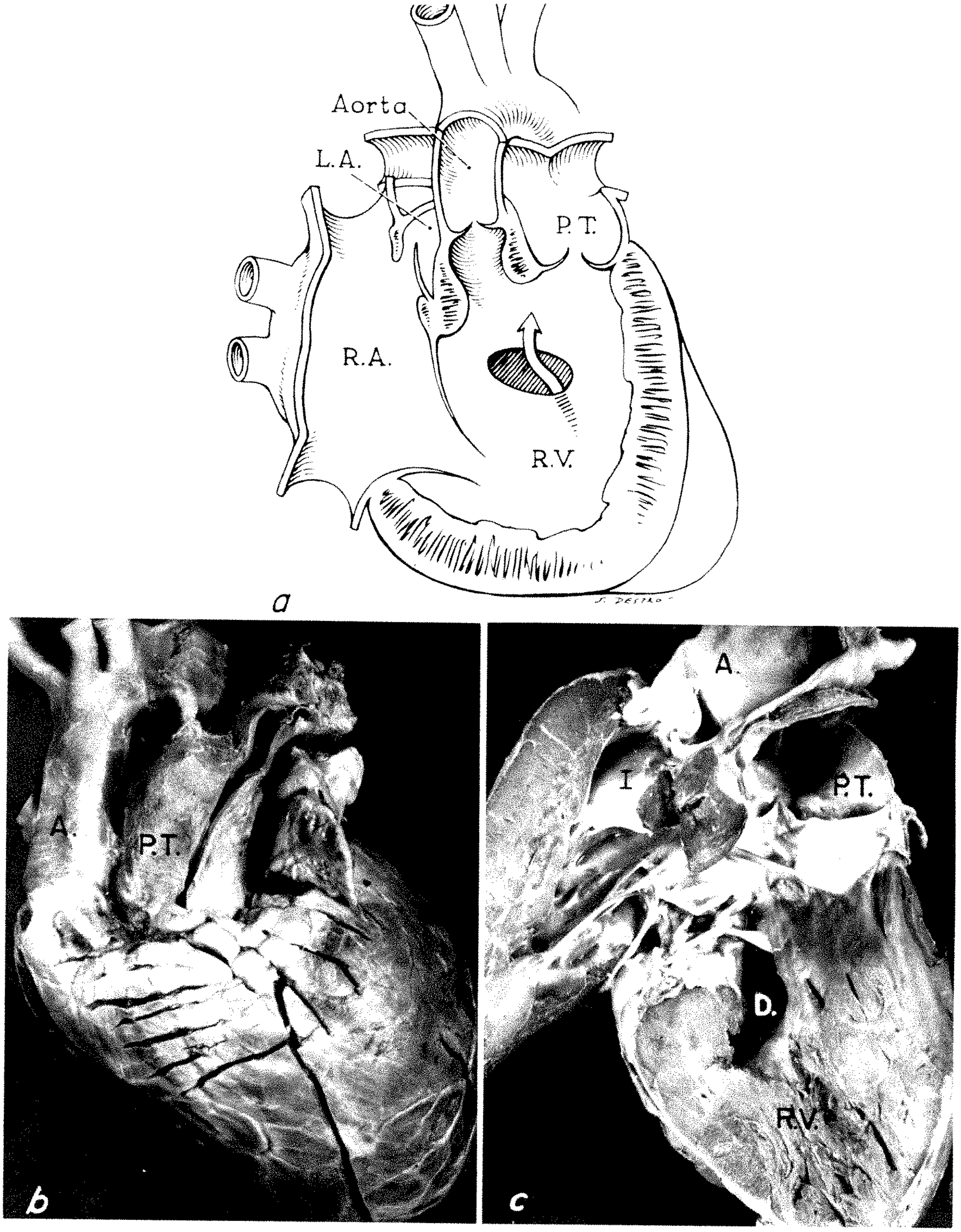

Fig. 23. Case xiv. Atypical example of origin of both great vessels from the right ventricle. (*a*) Diagrammatic portrayal of the malformation viewed from the right side of the heart. R.A. = right atrium; R.V. = right ventricle. A ventricular septal defect is the only outlet for the left ventricle. The pulmonary trunk (P.T.) arises from the right ventricle in a normal position, but not from an infundibular chamber. The aorta arises to the right of the pulmonary trunk from an infundibular chamber. The aortic valve is at a higher level than the pulmonary valve. (*b*) External view of the heart viewed from in front. The ascending aorta

ATYPICAL FORMS OF ORIGIN OF BOTH GREAT VESSELS FROM THE RIGHT VENTRICLE

ORIGIN OF AORTA FROM INFUNDIBULAR CHAMBER

Roentgenologic Observations.

Case XIV. Male, aged 25 years.

Roentgenograms of the thorax (Fig. 13*e*) showed mild cardiomegaly, enlargement of the right ventricle, pulmonary trunk and central pulmonary vasculature. There was an unusual, pulsatile, convex prominence of the upper right cardiac border which represented the infundibular chamber from which the aorta arose. No angiocardiographic studies were performed on this patient.

Pathologic Observations.

Pathologically, the heart showed a most unusual malformation (Fig. 23, *a–c*). The pulmonary trunk arose in a normal location, while the ascending aorta lay to the right of the pulmonary trunk and somewhat anterior to its normal location. The aorta arose from an infundibular-like subdivision at the right upper aspect of the base of the right ventricle. Within the ventricular septum lay a large defect which was entirely surrounded by muscle, the defect being more closely allied to the pulmonary valve than to the aortic valve. The aortic valve lay at a higher plane than did the pulmonary valve. Tricuspid valvular tissue was continuous with pulmonary valvular tissue.

CASE WITH SITUS INVERSUS

Roentgenologic Observations.

Case XV. Male, aged 4 years. (Case 3 of Ruttenberg and associates[7].)

Roentgenograms of the thorax and upper abdomen (Fig. 24, *a* and *b*) showed situs inversus, moderate cardiomegaly and attenuated pulmonary vasculature. There was a convex prominence of the left cardiac margin.

Angiocardiographic studies (Fig. 24, *c* and *d*) consisted of advancing a catheter from the left-sided inferior vena cava into the left-sided venous atrium, into the venous ventricle, and then through a ventricular septal defect into the outflow tract of the arterial ventricle. Injection of contrast material resulted in opacification of a small arterial ventricle and a larger venous ventricle. There was simultaneous opacification of both great vessels, the aortic and pulmonary valves lay at the same level and, in lateral view, the ascending aorta was transposed and lay distinctly anterior to the pulmonary trunk.

Pathologic Observations.

Pathologically, the specimen showed classic situs inversus (Fig. 25, *a* and *b*). The venous side of the heart was on the left and the arterial side on the right. In addition to a common atrium, there was atresia of the right-sided (arterial) atrioventricular valve. The left-sided (venous) atrioventricular valve led into a large chamber which lay on the left side and had the usual architectural features of a left ventricle. The right-sided ventricle (arterial in situs inversus) was hypoplastic and had the configuration of a right ventricle. The ascending aorta arose anteriorly and to the left of the pulmonary trunk, the latter lying posteriorly and being hypoplastic. In the ventricle from which the two great vessels arose, a spur of muscle, considered to be the parietal limb

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(A.) lies prominently to the right of the pulmonary trunk and more anteriorly than normal. It arises from an infundibular-like recess of the right upper aspect of the right ventricle. (*c*) Interior of right ventricle (R.V.). The ventricular septal defect (D.) lies more closely related to the origin of the pulmonary trunk than to that of the aorta (A.). The aortic valve lies at a higher plane than the pulmonary valve and the aorta arises from an infundibular-like division (I) of the right ventricle.

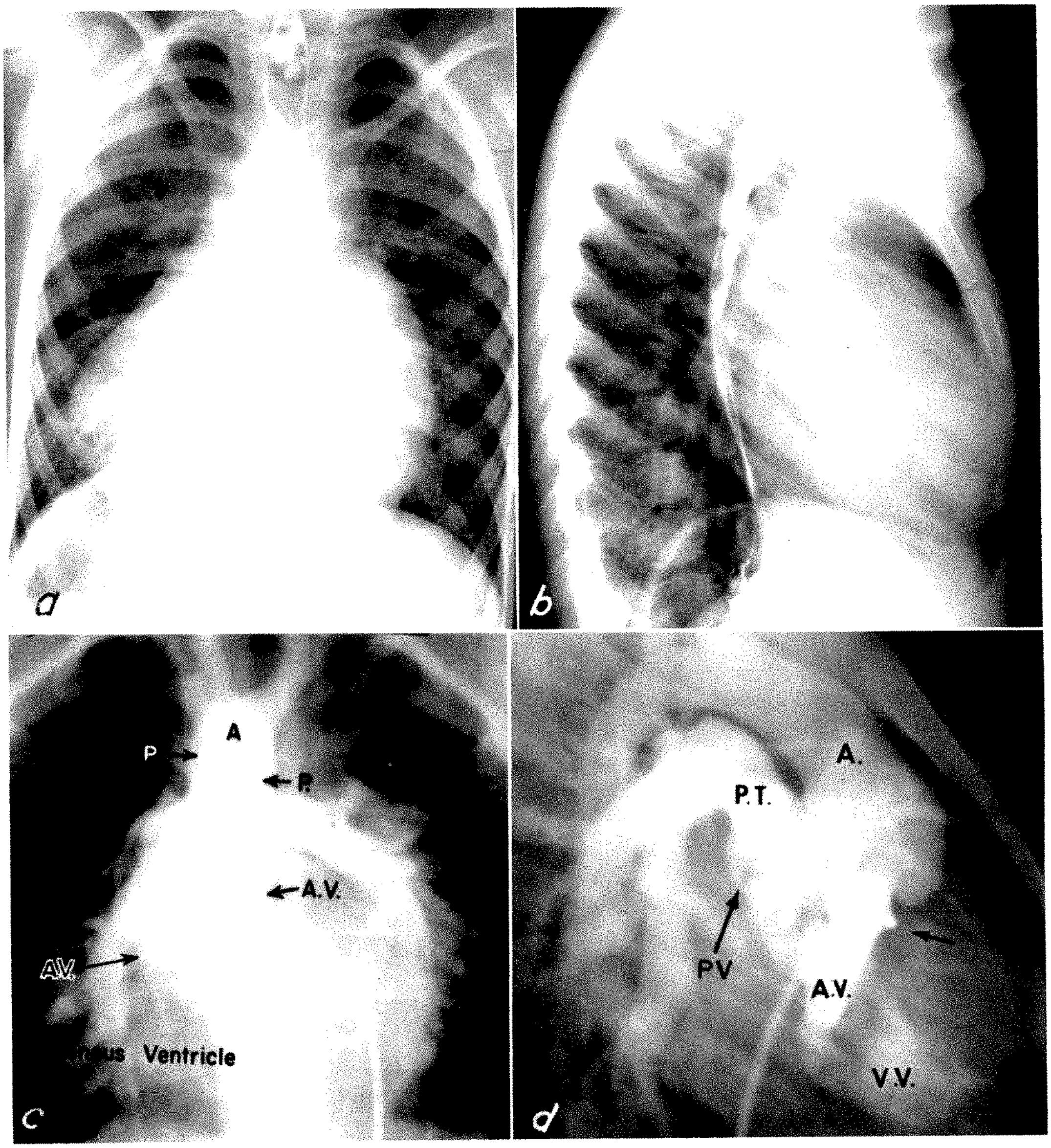

Fig. 24. Case xv. Origin of both great vessels from arterial ventricle in situs inversus. (*a* and *b*) Frontal and lateral roentgenograms of thorax showing situs inversus cardiomegaly and attenuated pulmonary vasculature. Deformity of barium-outlined esophagus caused by right-sided aorta. Striking prominence of the left cardiac margin caused by enlarged venous atrium. (*c* and *d*) Selective ventriculograms. Tip of catheter (arrow in *d*) positioned in outflow tract of arterial ventricle. Frontal and lateral views showing small arterial ventricle (A.V.) and venous ventricle (V.V.). Both great vessels are opacified; in lateral view the aorta (A.) lies anterior to the pulmonary trunk (P.T.). The aortic and pulmonary (PV) valves lay at the same level. In frontal view the pulmonary trunk (P.T.) lies directly posterior to the aorta (A.).

of the crista supraventricularis, separated the zones beneath the aortic and pulmonary valves. In addition, the subpulmonary zone was narrow and lined by thickened fibrous tissue. No continuity existed between the pulmonary valvular and atrioventricular valvular tissues. The ventricular septal defect, which was surrounded by muscle, lay beneath the level of the aortic valve.

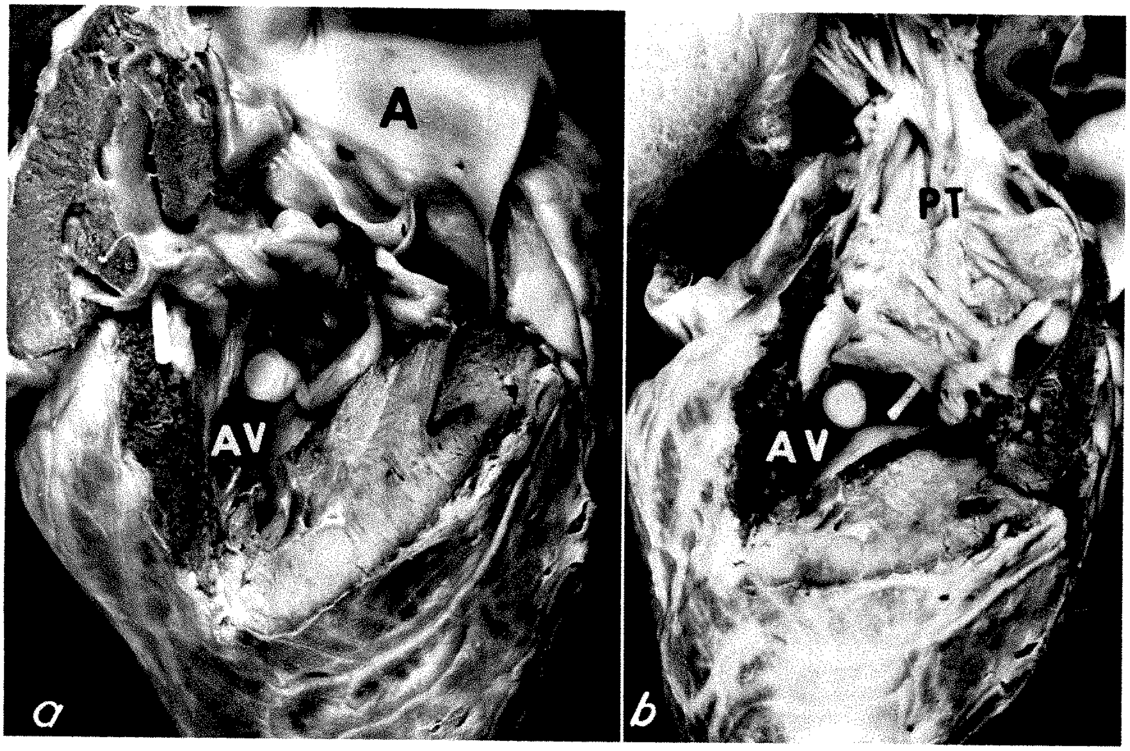

FIG. 25. Case XV. Situs inversus with origin of both great vessels from arterial ventricle. (Courtesy of Ruttenberg and associates and *Brit. Heart J.*[7]) (*a*) Interior of right-sided arterial ventricle (AV) which shows the features of a right ventricle. The aorta (A) arises from this ventricle. The larger probe is in the ventricular septal defect, the smaller probe leads to the pulmonary trunk. (*b*) The flap of tissue between the origin of the aorta and the origin of the pulmonary trunk has been reflected to the right to reveal the origin of the pulmonary trunk (PT) from the right-sided arterial ventricle. Beneath the pulmonary valve, fibrous thickening of the outflow tract of the right ventricle causes subpulmonary stenosis.

DISCUSSION

There is no uniform roentgenographic appearance for all cases of Type I origin of both great vessels from the right ventricle. When, however, those cases without a significant associated lesion are compared, there are certain nonspecific features in common. These include mild to moderate cardiomegaly and enlargement of the right ventricle, pulmonary trunk and central pulmonary vasculature.

Clinically and roentgenographically, patients with this malformation closely resemble those with ventricular septal defect with pulmonary hypertension. It would appear that, when the roentgenographic features deviate from this basic pattern, the alteration is secondary to the associated lesion.

The most striking angiocardiographic findings in this condition are simultaneous opacification of both great vessels from the right ventricle, a ventricular septal defect below the crista supraventricularis, aortic and pulmonary valves at, or nearly at, the same level and transposition of the aorta.

The degree of transposition is variable; in lateral angiocardiographic view, the proximal ascending aorta is usually superimposed over the posterior one-half or two-thirds of the proximal portion of the pulmonary trunk.

One striking angiocardiographic finding in frontal view which deserves emphasis is that at the base of the right ventricle, a "tongue-like" filling defect representing the crista supraventricularis separates the respective outflow tracts to the aorta and the pulmonary trunk. This appearance seems to distinguish this condition from the usual form of ventricular septal defect. The tendency for a catheter to enter the right ventricle when advanced from the aorta should arouse suspicion that both great vessels are arising from the right ventricle, but this finding is not specific.

In Type II, roentgenograms of the thorax usually show marked cardiomegaly which may be biventricular in nature, enlargement of the left atrium and striking prominence of the pulmonary trunk and pulmonary vasculature.

Angiocardiographically, as in Type I, there is simultaneous opacification of both great vessels from the right ventricle, but from the right ventricle there is preferential flow into the aorta. The aortic and pulmonary valves lay at or near the same level. In lateral views the aorta is usually superimposed over the pulmonary trunk; the ascending aorta is directed anteriorly throughout its course and the aortic valves are tilted anteriorly.

In frontal view a muscle spur of varying size is present in all cases and divides the base of the right ventricle into an outflow tract to each great vessel.

There are some cases of complete transposition with side-to-side relationship of the great vessels and other atypical cases of origin of both great vessels from the right ventricle which are difficult to separate clinically and angiocardiographically from the classic Type II cases. It appears that this distinction cannot be made ante mortem.

The demonstration of coarctation and hypoplasia of a portion of the aortic arch in a case of cyanotic heart disease in infancy, associated with marked cardiomegaly, enlargement of the pulmonary trunk and increased vasculature, should arouse suspicion of Type II origin of both great vessels from the right ventricle.

SUMMARY

The roentgenographic findings in Type I cases of origin of both great vessels from the right ventricle are similar to those seen in patients with ventricular septal defect and pulmonary hypertension; namely, right ventricular enlargement and striking prominence of the pulmonary trunk and central pulmonary vasculature.

The angiocardiographic findings, however, appear to be diagnostic and include the following: (1) opacification of both great vessels from the right ventricle, (2) pulmonary and aortic valves at the same level, (3) partial transposition of the aorta in lateral view and (4) a "tongue-like" filling defect at the base of the right ventricle which represents the parietal limb of the crista and which forms two outflow tracts. The latter feature is seen in frontal view and is considered specific; it has not been seen in frontal angiocardiograms in cases of ventricular septal defect with pulmonary hypertension.

The roentgenographic and angiocardiographic findings in Type II are, for the most part, similar, but there are important differences. On conventional roentgenograms the cardiomegaly is more striking, left atrial enlargement is usually present and there may be a suggestion of left ventricular enlargement. The flow of contrast material from the right ventricle is primarily into the aorta. In lateral view the aorta is more obviously transposed than in Type I and the aortic valve is tilted anteriorly. Coarctation of the aorta and/or hypoplasia of a portion of the aortic arch is commonly present.

Certain other anomalies in which transposition occurs may be indistinguishable angiocardiographically from Type II.

Atypical examples of origin of both great vessels from the right ventricle have also been shown.

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SELECTIVE ANGIOCARDIOGRAPHY FOR DIAGNOSIS OF CONGENITAL CARDIAC DEFECTS IN INFANCY*

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MORTALITY from congenital heart disease is extremely high during the first weeks of infancy. More than 60 per cent of these infants succumb in the first year, half of them during the first month of life.[2,3] Diagnostic techniques capable of defining the anatomic malformations with precision, therefore, are of utmost importance. Most of the infants with symptoms in the first few weeks of life are so ill that only the simplest procedure able to convey enough anatomic detail for the surgeon is warranted.

A review of the literature reveals a few reports of selective angiocardiography in infants less than 1 month of age. Some investigators have pointed to the increased hazards of angiocardiographic studies in extremely young infants.[5] The tendency has been to postpone diagnostic studies until the child is older and is a better diagnostic risk.

A review of the angiocardiographic studies in 17 infants with the use of a Schönander-Elema rapid biplane film changer has shown the value of this method as a primary diagnostic procedure. Our experience with this technique forms the basis of this report.

MATERIAL AND METHOD

Seventeen infants were studied, whose ages ranged from 3 to 18 days at the time of the first angiocardiographic procedure (Table 1). All were clinically symptomatic. Anoxemia and pulmonary congestion were the two most prominent symptoms. The site of injection of angiocardiographic contrast material was established by clinical examination, plain roentgenogram, and electrocardiogram. The procedure was performed at least 3 hours after feeding. No anesthesia was used, although on rare occasions a small dose of morphine sulfate was administered to a restless patient. Oxygen was administered continuously to those infants who were severely cyanotic.

All intracardiac injections were performed through a No. 4 or No. 5 Rodriguez-Alvarez catheter, using a Gidlund injector with a firing pressure of 5 to 10 kg. per cm.^{2} Hypaque, 75 per cent, was used for the intracardiac injection. It was usually administered on the basis of 1.2 cc. per kg. of body weight. Retrograde arterial injections were performed manually through a No. 17 or a No. 18 Lindemann needle inserted into the brachial artery. For this study, 50 per cent hypaque was administered on the basis of 1 cc. per kg. of body weight. All intracardiac catheters were guided to the injection sites under fluoroscopic control with continuous monitoring of pressure.

RESULTS

In 12 of the 17 patients the procedure established the diagnosis precisely (Fig. 1 through 3, inclusive). Two patients in whom the presenting sign was severe cyanosis demonstrated no cardiac abnormalities on angiocardiographic examination. In retrospect, evidence of hyaline membrane disease was seen on plain roentgenograms in 1 patient. Cyanosis disappeared in the other patient and was presumed to have been related to an elevated hemoglobin which later returned to normal. Another patient with suspected aortic atresia was

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TABLE I

CLINICAL DATA AND ANGIOCARDIOGRAPHIC RESULTS IN 17 INFANTS EXAMINED IN THE FIRST 18 DAYS OF LIFE

Case Sex Age Weight (gm.)	Clinical Diagnosis	Condition of Patient	Site of Injection	Angiocardiographic Diagnosis	Postoperative or Postmortem Diagnosis	Therapy	Results
1. M 3 days 2,778	C.C.H.D.; transposition or hypoplastic left heart	Cyanosis; dyspnea; no pulses in legs	Left atrium	Complete transposition; V.S.D.; P.D.A.	Transposition of great vessels with large interventricular septal defect	Died during surgery	
2. F 3 days 2,622	C.C.H.D.	Cyanosis; no failure; improved with oxygen	Right ventricle	Normal; small physiologic P.D.A.	No surgery; presumed to be hyaline membrane disease	Supportive	Excellent recovery
3. F 5 days 3,473	Pulmonary atresia	Progressive cyanosis	Right atrium	Symmetric liver; absent spleen; cor biloculare; P.S.	Angiocardiographic diagnosis confirmed at surgery	Glenn procedure[4,6]	Died postoperatively
4. M 7 days 3,657	Transposition	Severe cyanosis and failure	Right ventricle	Transposition; V.S.D.; P.D.A.	Transposition; V.S.D.; closed ductus	Senning procedure[7]	Died postoperatively
5. F 8 days 3,374	Hypoplastic left heart	Severe cyanosis and failure	Left ventricle	Pulmonary atresia; V.S.D.; P.D.A.	Ebstein's anomaly of tricuspid valve; patent foramen ovale	Surgical procedure attempted	Died postoperatively
6. M 9 days 4,380	Aortic atresia; pulmonary atresia	Slight cyanosis; failure	Brachial artery	Normal	No surgery	Supportive	Excellent recovery
7. M 9 days 3,827	C.C.H.D.; possible pulmonary atresia	Cyanosis; anoxic seizures	Right ventricle	Transposition; V.S.D.; P.S.; P.D.A.	Diagnosis confirmed	Blalock-Hanlon procedure[1]	Died postoperatively
8. M 10 days 2,707	Coarctation; possible P.D.A.	Failure; critical condition	Brachial artery	Coarctation, post-ductal; P.D.A.	No postmortem examination	Supportive	Died
9. M 10 days 4,200	C.C.H.D.	Cyanosis; mild failure	Right atrium	Transposition; P.S.; right aortic arch; A.S.D.	Transposition; A.S.D.; P.D.A.	Supportive; died before operation could be done	Postmortem examination
10. M 12 days 4,125	Total anomalous pulmonary venous return or transposition	Cyanosis	Right ventricle	No abnormality found	No proof; developed normally	None	Excellent
11. M 12 days 2,835	Transposition of great vessels	Cyanosis; failure; critical condition	Right atrium	Transposition; P.D.A.; patent foramen ovale	Angiocardiographic diagnosis confirmed by postmortem examination	Supportive	Died
12. F 13 days 2,098	Pulmonary atresia with A.S.D.	Severe cyanosis; critically ill	Right atrium	Pulmonary atresia; A.S.D.; P.D.A.; corrected transposition	Pulmonary atresia; V.S.D.; A.S.D.; partial anomalous pulmonary venous return	Supportive	Died; postmortem examination

C.C.H.D. = Cyanotic congenital heart disease.
V.S.D. = Ventricular septal defect.
P.D.A. = Patent ductus arteriosus.
P.S. = Pulmonary stenosis.
A.S.D. = Atrial septal defect.

TABLE I (*Continued*)

Case Sex Age Weight (gm.)	Clinical Diagnosis	Condition of Patient	Site of Injection	Angiocardiographic Diagnosis	Postoperative or Postmortem Diagnosis	Therapy	Results
13. F 15 days 3,799	Transposition	Cyanosis; mild failure	Right ventricle	Transposition; intact ventricular septum; P.D.A.	Transposition; P.D.A.	Blalock-Hanlon procedure[1]	Improved
14. M 15 days 3,090	C.C.H.D.; probable transposition	Mild cyanosis; mild failure	Right ventricle	V.S.D. with origin of both great vessels from right ventricle	Not proved; catheterization showed V.S.D.; severe pulmonary hypertension	Supportive only; operative lesions ruled out	Still alive, in fair condition
15. F 17 days 2,722	Aortic atresia	Cyanosis; apneic episodes; critically ill	Pulmonary artery	A.S.D. left to right; P.D.A.; coarctation	No surgery or postmortem examination	Supportive	Died; no postmortem examination
16. F 18 days 3,671	Transposition or hypoplastic left heart	Cyanosis and failure	Brachial artery; left atrium	Complete interruption of aortic arch; P.D.A.; V.S.D.; subclavian artery arising from descending aorta	Interruption of aortic arch with subclavian arteries arising from descending aorta	Died during surgery	
17. M 18 days 3,475	Coarctation or P.S.	Cyanosis; episode of failure	Brachial artery	Postductal coarctation; no P.D.A.	Coarctation of aorta	Surgical repair of coarctation	Good recovery

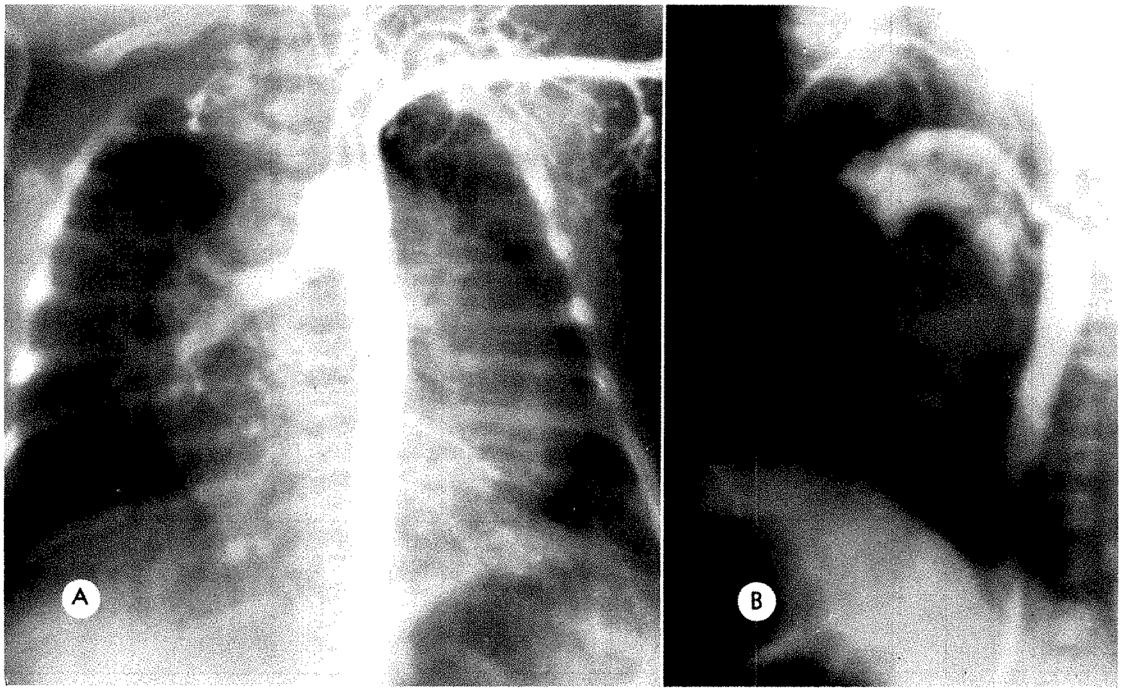

FIG. 1. (*A* and *B*) Injection in brachial artery revealed a patent ductus arteriosus and postductal coarctation. Evidence of early dense filling of pulmonary artery in both the posteroanterior and lateral projections. Coarctation is seen in the lateral view.

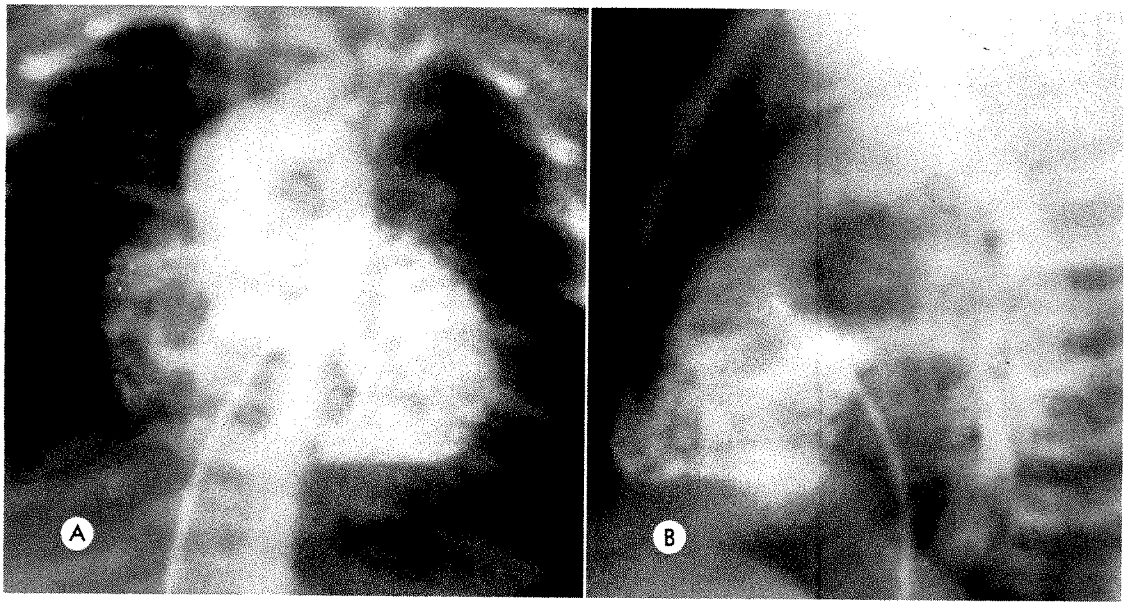

Fig. 2. (*A* and *B*) Transposition of great vessels with anterior position of aorta and intact ventricular septum. Right ventricular injection. A small patent ductus arteriosus is present. This 15 day old infant improved after surgical creation of an atrial septal defect.

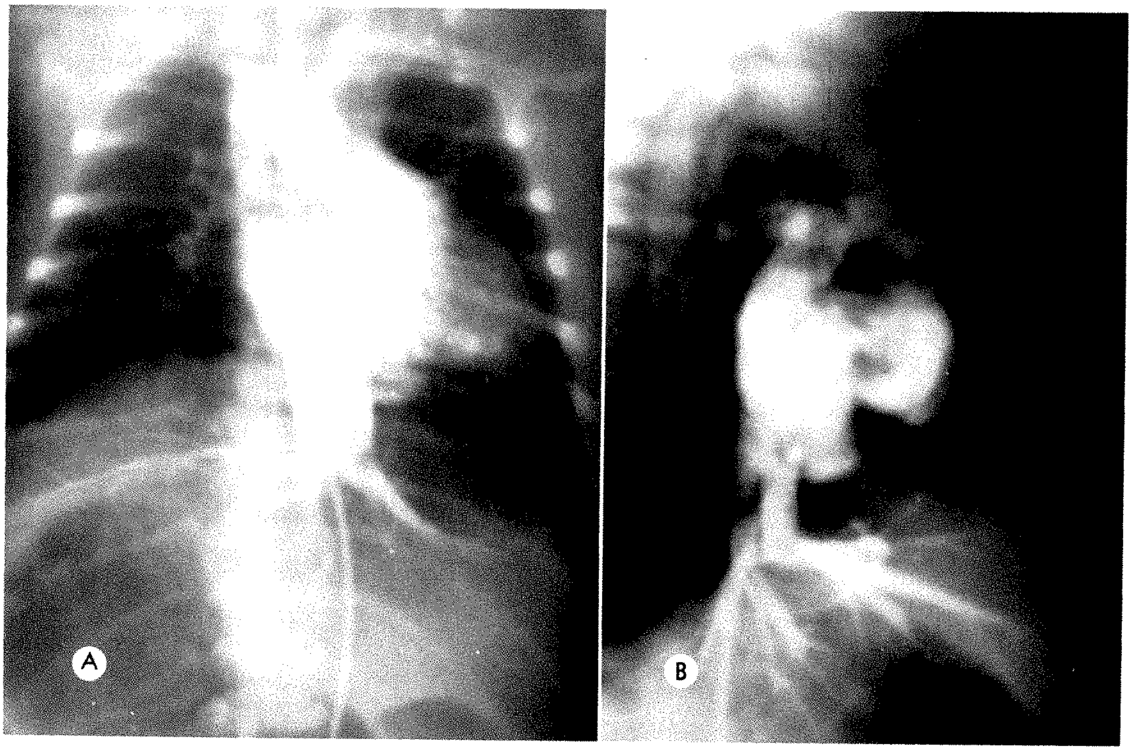

Fig. 3. (*A* and *B*) Complicated defect with situs inversus of abdominal viscera, symmetric liver, and absent spleen. Levocardia with left-sided inferior vena cava, cor biloculare, corrected transposition of the aorta, and pulmonary stenosis.

found angiocardiographically to be normal on both sides of the heart. This patient has improved clinically and the probable cause of symptoms has been attributed to a myocarditis. The angiocardiographic exclusion of operable heart disease greatly facilitated the medical management of these 3 patients.

A diagnosis was made in a fourth infant of "origin of both great vessels in the right ventricle." Confirmation of this diagnosis must await surgical intervention or postmortem examination. Only once did selective angiocardiography lead to an erroneous diagnosis. This occurred in an infant in whom the catheter was passed from the right atrium through an atrial septal defect and into the left ventricle. The position of the catheter was not appreciated. Contrast material injected at this site passed directly into the aorta, which resulted in a diagnosis of pulmonary atresia with ventricular septal defect, not confirmed at operation. Postmortem examination revealed an Ebstein's anomaly of the tricuspid valve.

No complications resulted from the angiocardiographic procedure except in 1 infant in whom a wound developed at an arterial cut-down site.

DISCUSSION

Selective angiocardiography as the primary diagnostic method in extremely early infancy has proved satisfactory. The additional studies that are usually obtained during catheterization of the right side of the heart have not proved necessary. In general, cardiac catheterization alone does not establish an accurate anatomic diagnosis of the congenital cardiac defect in symptomatic infants at these early ages. Defects such as transposition of the great vessels, single ventricle, tricuspid atresia, and the group of cardiac defects comprising the hypoplastic left heart syndrome usually cannot be accurately diagnosed from cardiac catheterization alone. Pressure and oxygen data are difficult to evaluate in this age group. The manipulations necessary for the catheter to enter the pulmonary artery increase the hazard of this procedure. For these reasons, primary reliance has been placed on selective angiocardiography. The position of the catheter tip is monitored by pressure recording and occasionally blood is withdrawn for an oxygen determination, but otherwise, no additional procedures have been undertaken. In general, injection of contrast material in cyanotic infants has been performed from the right ventricle or right atrium. When a left-sided lesion is suspected, a left atrial or retrograde brachial injection has been used. When a subsequent study was considered indicated, it was performed on another day.

The data presented do not support the concept that selective angiocardiography *per se* in the extremely young age group is more hazardous than in older children. Obviously, other important factors, particularly the clinical condition of the patient, must be considered in each individual case. The safety of the procedure appears to be enhanced by the unanesthetized state, a short procedure time, little blood loss, and minimal manipulation of the catheter.

CONCLUSION

Selective angiocardiography is the method that best supplies the diagnostic accuracy needed for emergency surgical procedures of severe congenital heart disease in the neonatal period.

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THE ROENTGENOLOGIC FINDINGS IN LEFT VENTRICULAR-RIGHT ATRIAL COMMUNICATION*

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LEFT ventricular-right atrial (LV-RA) communication is an uncommon variant of ventricular septal defect. The clinical findings alone are not diagnostic, but mimic those of other more common congenital malformations of the heart, namely, atrial septal defect, ventricular septal defect, and defects considered as part of the atrioventricular commune group of malformations.

In some individuals with LV-RA communication, the clinical features may suggest coexistence of an atrial septal defect and a ventricular septal defect. Moreover, cardiac catheterization and indicator dilution techniques merely reveal evidence of a left-to-right shunt at the atrial level and do not establish the anatomic diagnosis.

The specific anatomic diagnosis of LV-RA communication depends upon the use of selective left ventriculography.

It is the purpose of the authors to describe the features, with particular emphasis upon the roentgenologic findings, in 14 anatomically proved cases of LV-RA communication which were observed at the University of Minnesota Hospitals.

In 11 of these cases, surgical correction was done. The surgical experience of 10 of the cases formed the basis for one report[8] and the eleventh case was described in 2 other reports.[9,16] Four deaths occurred postoperatively but necropsy was done in only 1, the eleventh case mentioned above. This patient, a 13 year old girl, died 7 months following operation. In addition to the 11 surgical cases mentioned, this study included 3 not operated on fatal cases, on each of which necropsy was performed, making a total of 14 cases which comprise the study reported here.

Anatomic facts were derived from the observations made during operation in the 11 operated cases and from necropsy in 4 cases. The latter include the 3 cases in this study upon which surgical intervention had not been attempted and the aforementioned surgical case in which necropsy was also done.

PATHOLOGIC ANATOMY

The pathologic anatomy in the 3 cases in which operation was not performed was similar and will, therefore, be described together. The pathologic anatomy in the case in which surgical correction was performed showed additional pathologic features and will be described separately.

PATHOLOGIC ANATOMY IN NONSURGICAL CASES

The pathologic anatomy in the aforementioned 3 cases showed an abnormal communication between the left ventricle and right atrium (namely, a left ventricular-right atrial communication).

External examination revealed the two great vessels to be normally related. The aorta took origin from the left ventricle and the pulmonary trunk took origin from the right ventricle.

Each specimen showed dilatation and hypertrophy of both of its ventricles and dilatation of the atria, particularly of the right. The right atrial dilatation was considerably greater than that observed in most instances of ventricular septal defect. The right ventricular dilatation was similar to that seen with the usual atrial septal defect.

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The mitral valve and the venous connections with the atria were normal.

In one specimen, a small atrial septal defect of the fossa ovalis type was present in addition to the LV-RA communication. A valvular competent foramen ovale was identified in each of the other 2 specimens studied. The ductus arteriosus was found obliterated in each specimen.

The LV-RA communication took the form of a ventricular septal defect which opened into a cleft in the tricuspid valve.

From the right ventricular view, the ventricular septal defect was located postero-inferior to the parietal limb of the crista supraventricularis in each of the 3 cases. It did not extend along the septal limb of the crista, as in some examples of isolated ventricular septal defect, but opened into a space formed by a cleft in the tricuspid valve at the junction of the septal and anterior leaflets of that valve (Fig. 1, *a–d;* and 2, *a* and *b*).

In each of the 3 cases, the edges of the cleft in the tricuspid valve were adherent to the margins of the ventricular septal defect, thereby causing a communication between the left ventricle and the right atrium.

In 2 cases, the anterior leaflet of the tricuspid valve just beside the cleft showed an aneurysm (Fig. 1, *b* and *c*) which presented into the lower aspect of the right ventricular infundibulum. In the third specimen, there was secondary thickening and a roughened corrugated surface to the anterior tricuspid leaflet (Fig. 2*a*), but no aneurysm.

In each case, when the defect was viewed from the left ventricular side, its center lay below the junction of the right and posterior aortic cusps (Fig. 1*d* and 2*b*). It was separated from the aortic valve and from the anterior leaflet of the mitral valve by a thin rim of septal tissue. In contrast to ventricular septal defect of the atrioventricular commune type,[13] the defects in our cases did not include a large component of the anterior aspect of the ventricular septum. From the left ventricle, tricuspid valvular tissue was seen to be adherent to the anterior and the posterior margins of the defect.

PATHOLOGIC ANATOMY IN SURGICAL CASE

The pathologic anatomy in the 13 year old girl in whom surgical correction of the LV-RA communication had been performed revealed an enlarged and hypertrophied right atrium and right ventricle. The great vessels were normally interrelated and the venous connections were normal.

From the right ventricular view, there was an aneurysm of the membranous portion of the ventricular septum which lay behind the crista supraventricularis, between the anterior and septal leaflets of the tricuspid valve. The LV-RA communication was represented by an opening in the aneurysm of the membranous septum. The edges of the opening were fused to the edges of an accessory opening in the septal leaflet of the tricuspid valve. In contrast to the aforementioned 3 cases, there was no cleft at the junction of the septal and anterior leaflets of the tricuspid valve.

From the left ventricular view, the aneurysm of the membranous portion of the ventricular septum originated as an orifice, 5 mm. in diameter, centered beneath the right half of the anterior cusp of a mildly stenotic bicuspid valve. Just below the aneurysm of the membranous portion, a rim of fibrous tissue (partially resected at operation) protruded into the lumen of the left ventricular outflow tract and caused subaortic obstruction.

In addition, the left side of the heart showed (1) a modified "parachute mitral valve" which was formed by the close apposition of two papillary muscles and their chordae inserting into the two mitral leaflets, (2) a nonobstructive supravalvular

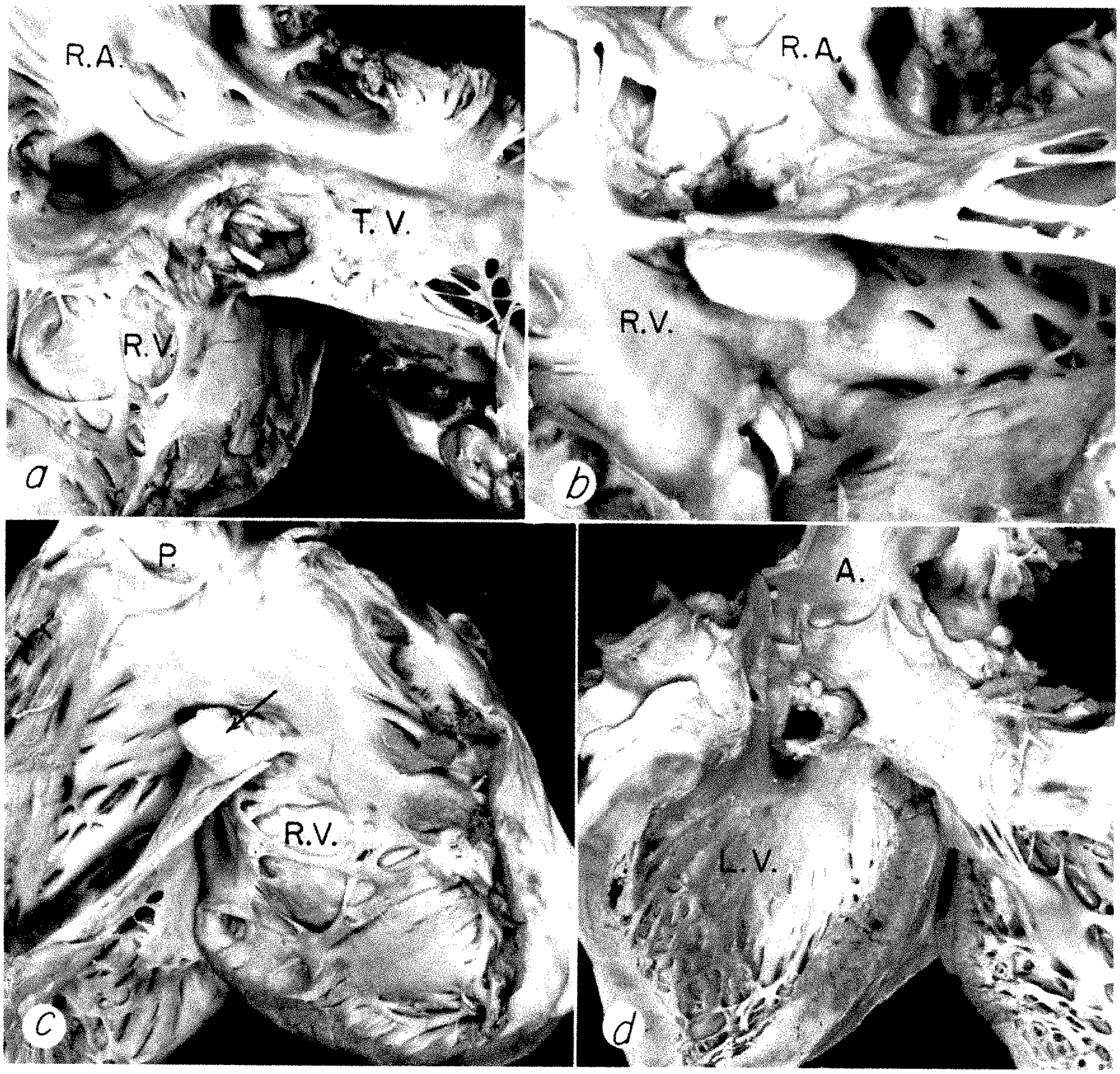

Fig. 1. Left ventricular-right atrial communication in a 10 year old boy. (*a*) Right atrium (R.A.) and right ventricle (R.V.). The probe lies in a cleft at the junction of the septal and anterior leaflets of the tricuspid valve (T.V.) through which the right atrium communicated with the left ventricle. Beneath the tip of the probe is the aneurysmal sac of the anterior tricuspid leaflet. (*b*) Close-up view of the cleft in the tricuspid valve and adjacent structures. The anterior leaflet is viewed in profile and shows the aneurysm projecting from its ventricular aspect. The dark zone formed in the cleft of the tricuspid valve represents the communication of the right atrium with the left ventricle. Fibrous thickening of the valvular tissue around the abnormal communication. (*c*) Right ventricle (R.V.) and pulmonary trunk (P.). The aneurysm (arrow) of the anterior leaflet of the tricuspid valve presents into the right ventricle beneath the crista supraventricularis. No communication between the left ventricle and the right ventricle is present. (*d*) Left ventricle (L.V.) and the ascending aorta (A.) Beneath the aortic valve and separated from the valve by septal tissue is a ventricular septal defect which communicated with the right atrium. Tissue at the anterior and posterior boundaries of the defect represents adherent tricuspid valvular tissue.

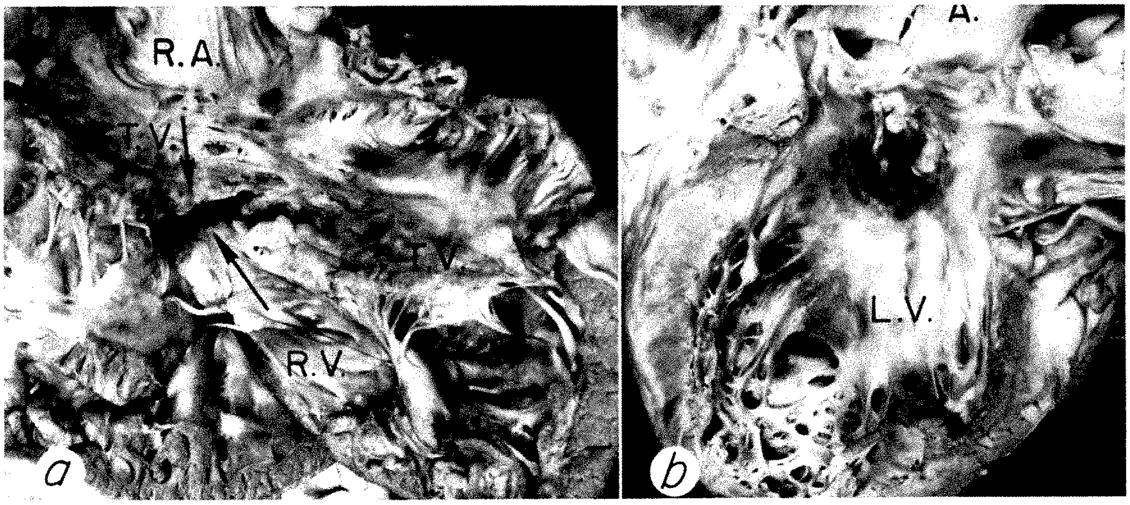

Fig. 2. Left ventricular-right atrial communication in a 12 year old girl. (*a*) Right atrium (R.A.) and right ventricle (R.V.). In the tricuspid valve (T.V.) between the arrows is a cleft which lies at the junction of the septal and anterior leaflets. The edges of the cleft in the tricuspid valve are adherent to the edges of an underlying ventricular septal defect, thereby creating a communication between the left ventricle (out of view in this illustration) and the right atrium. There is secondary fibrous thickening of the atrial aspect of the tricuspid valve, especially of the anterior leaflet. (*b*) Left ventricle (L.V.) and the ascending aorta (A.). The defect in the ventricular septum lies inferior to the commissure between the right and posterior aortic cusps. Tissue separates the ventricular septal defect from the aortic valve. As in Figure 1, *a-d*, tricuspid tissue is adherent both to the anterior and posterior margins of the ventricular septal defect.

ring of the left atrium, and (3) a mild degree of aortic coarctation.

CLINICAL FEATURES

Eight of the 14 patients were female and 6 were male. Their ages ranged from 2 years to 24 years. Nine of the patients were between 7 and 13 years of age. The ages of the remaining 5 were 2, 3, 4, 17 and 24 years, respectively.

Each patient was acyanotic at birth and in the neonatal period. A loud, harsh murmur, similar in location and timing to that of the usual ventricular septal defect, was heard. Signs of congestive cardiac failure were observed in 4 of the patients during infancy.

Electrocardiographic studies revealed signs of right atrial enlargement in 8 cases. Signs of various degrees of biventricular hypertrophy were observed in 12 and evidence of isolated right ventricular hypertrophy was encountered in 2. Two cases showed severe left axis deviation, and the electrocardiogram in neither of these could be differentiated from that in patients with persistent common atrioventricular canal.[3]

Right-sided cardiac catheterization showed a significant increase in oxygen saturation at the right atrial level in each case. The majority showed mild to moderate elevations of pulmonary hypertension. The pulmonary arterial pressure in the latter patient was equivalent to the systemic arterial pressure.

Surgical correction was performed in 11 patients, 7 of whom survived and are free of symptoms.

ROENTGENOGRAPHIC FINDINGS

RELATIONSHIP AND SIZE OF THE GREAT VESSELS

In 12 of the 14 cases studied, the shadows of the thoracic aorta and pulmonary trunk appeared normal, indicating a normal relationship between the two great vessels. In the remaining 2 cases, although the great vessels were found to be normally related at the time of cardiac catheterization and operation, there were certain signs in the thoracic roentgenogram which suggested the presence of transposed great vessels (Fig. 3, *a* and *b*). In both cases the superior mediastinum was unusually narrow, and the usual densities of the aortic knob and of the pulmonary trunk were not apparent.

The aortic knob was normal in size in 3 cases and small or hypoplastic in the remaining 11 cases (Fig. 4, *a-f*). In no case, was the aortic knob enlarged.

In 8 of the 12 cases in which the pulmonary trunk was apparent, there was pronounced enlargement of this structure, and moderate enlargement in the remaining 4 (Fig. 4, *a-f*).

PULMONARY VASCULARITY

In each of the 14 cases studied, the pulmonary vasculature was of increased prominence, but of degrees varying from moderately to considerably prominent in 13 cases and only mildly prominent in one (Fig. 3, *a* and *b;* and 4, *a-f*).

In 11 of the 13 cases with moderate or considerable increase in prominence of the pulmonary vascularity, the characteristics of the vessels in the peripheral two-thirds of the lungs indicated a high flow-low resistance situation, whereas in 2 cases the appearance of the vessels in the peripheral two-thirds of the lungs suggested severe vascular occlusive changes. In 1 of the latter 2 cases the findings were consistent with the cardiac catheterization observations of high pulmonary arterial pressure; in the other, cardiac catheterization indicated only moderate elevations of pulmonary arterial pressure and of pulmonary vascular resistance.

The right pulmonary hilus was partially obscured by the right cardiac border in 2 of the 14 cases (Fig. 5, *a* and *b*). In 9 of the remaining 12 cases, the right hilus was observed to be slightly lower than the left hilus and in 2 cases, the right hilus was in the same horizontal body level (Fig. 4*a*).

CARDIAC SILHOUETTE

In each of the 14 cases, cardiomegaly, varying from moderate to severe in degree, was observed. The cardiac silhouette in the frontal projection could be described as "globular" in the majority of cases (Fig. 3, *a* and *b;* 4, *a-f;* and 5, *a* and *b*).

In roentgenograms studied in frontal view, the contours formed by the right and left sides of the heart were of particular significance.

In 11 of the 14 cases, the right cardiac

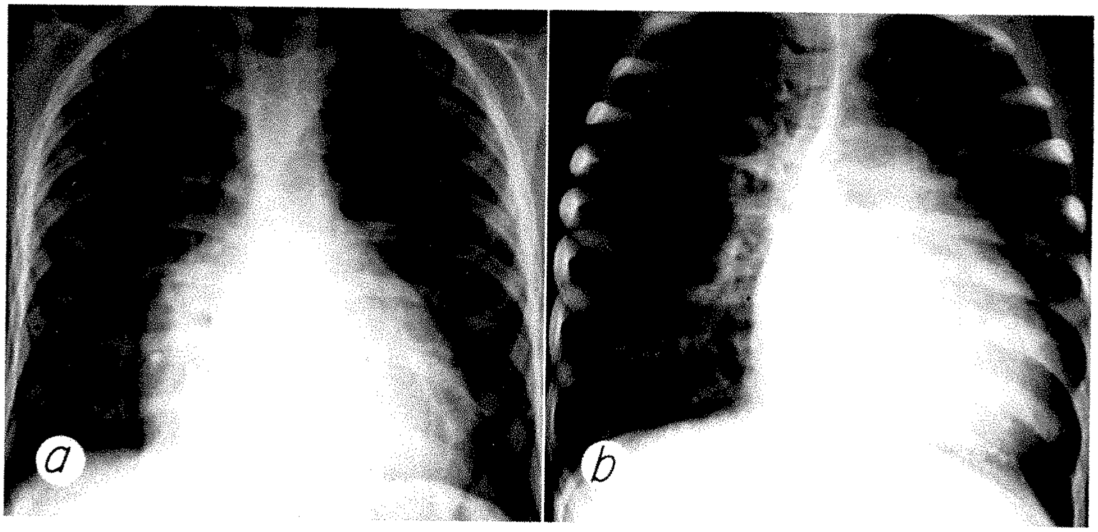

FIG. 3. Frontal thoracic roentgenograms. (*a*) Four year old boy. The superior mediastinum is narrow and the normal relationship of the great vessels is inapparent. (*b*) Ten year old boy. The right hilus is at the same level as the left. Contour resembles corrected transposition although great vessels were normally related.

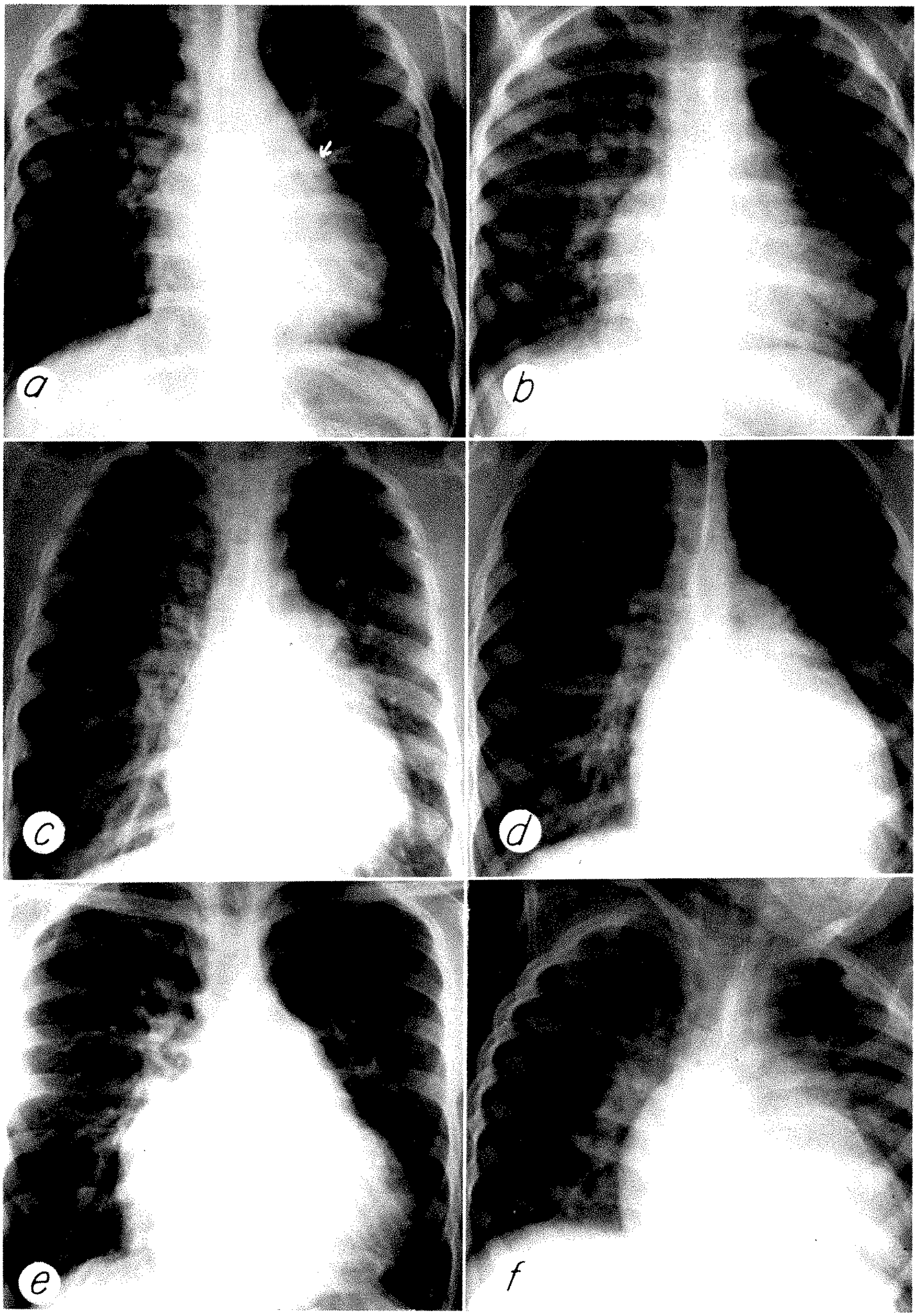

FIG. 4. Frontal thoracic roentgenograms in 6 cases of LV-RA communication. (*a*) Seven year old boy. Arrow points to bulge of left atrial appendage; (*b*) 3 year old girl; (*c*) 10 year old girl; (*d*) 19 year old man; (*e*) 17 year old boy; (*f*) 2 year old boy.

border was unusually prominent (Fig. 1*a* and 5*a*), a feature considered to represent the dilated right atrium. In 2 cases, there was an additional prominence at the upper aspect of the right cardiac border which, at the time of surgical correction, proved to have been caused by an enlarged right atrial appendage (Fig. 5*b*). The left cardiac border was also rounded in a convex manner, suggesting left ventricular enlargement. In 10 of the 14 cases, the left cardiac border was smooth and formed a distinct junction with the density of the pulmonary trunk. In 3 cases, however, there was an additional bulge below the pulmonary trunk which was consistent with an enlarged left atrial appendage (Fig. 4*a*). Enlargement of the pulmonary trunk, of the left atrial appendage and of the left ventricle resulted in 3 convexities of varying size along the left cardiac border. In one adult, the contour of the heart was similar to that seen in acquired mitral stenosis.

Signs of left atrial enlargement were observed in the frontal view in 7 cases.

In lateral roentgenograms, the anterior aspect of the superior mediastinum was unusually full in 11 of the 14 cases (Fig. 6*a*). Moreover, there was protuberance of the sternum owing to the enlarged right-sided cardiac structures in 10 of these 11 cases.

There were signs of left atrial enlargement in 11 of 14 cases. Three of these 11 cases showed mild enlargement, whereas 8 cases showed moderate enlargement (Fig. 6, *a* and *b;* and Fig. 7*a*). Left ventricular enlargement was additionally shown in 6 of the latter 8 cases. When the enlargement or dilatation was distinct, there was a distinct prominence of the curvature of the posterior and lateral borders of the ventricle. As a result, the enlarged left ventricle projected beyond the lower aspect of the barium-filled esophagus (Fig. 7*a*). Thus, among the majority of cases with a considerable degree of right-sided enlargement, signs of left-sided enlargement were additionally observed. The significance of this finding will be discussed in the *Comment.*

When the roentgenograms were viewed in the left anterior oblique projection, right-sided cardiac enlargement was observed in each of the 14 cases studied (Fig. 7*b*). This is a significant observation since, in a few cases, right-sided cardiac enlargement was not observed in either the frontal or lateral projections.

Left ventricular enlargement was evident

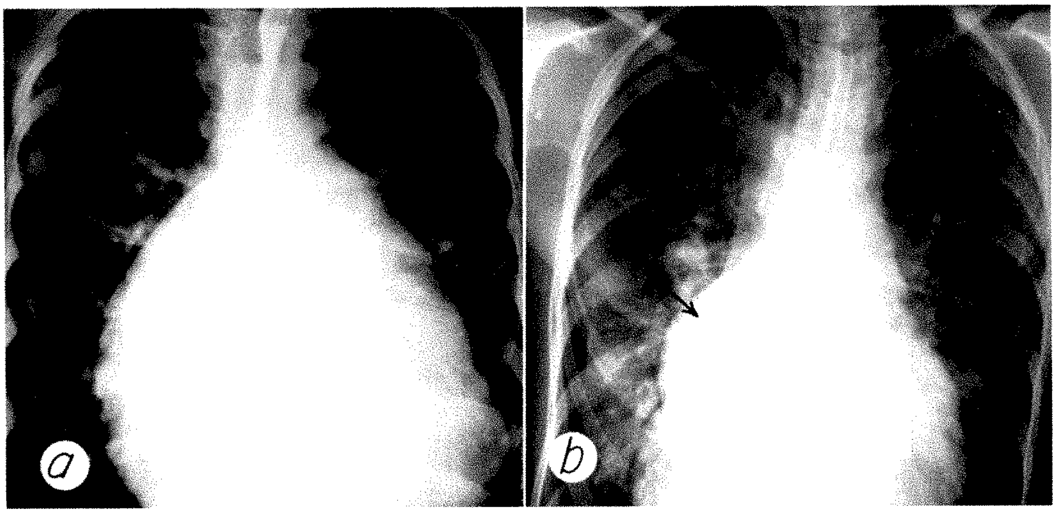

Fig. 5. Frontal thoracic roentgenograms. (*a*) Thirteen year old girl. There is considerable right-sided cardiac enlargement. The right hilus is obscured. (*b*) Twelve year old girl. There is slight rotation of the patient. The prominent bulge of the right side of the heart (arrow) proved to be an enlarged right atrial appendage at necropsy.

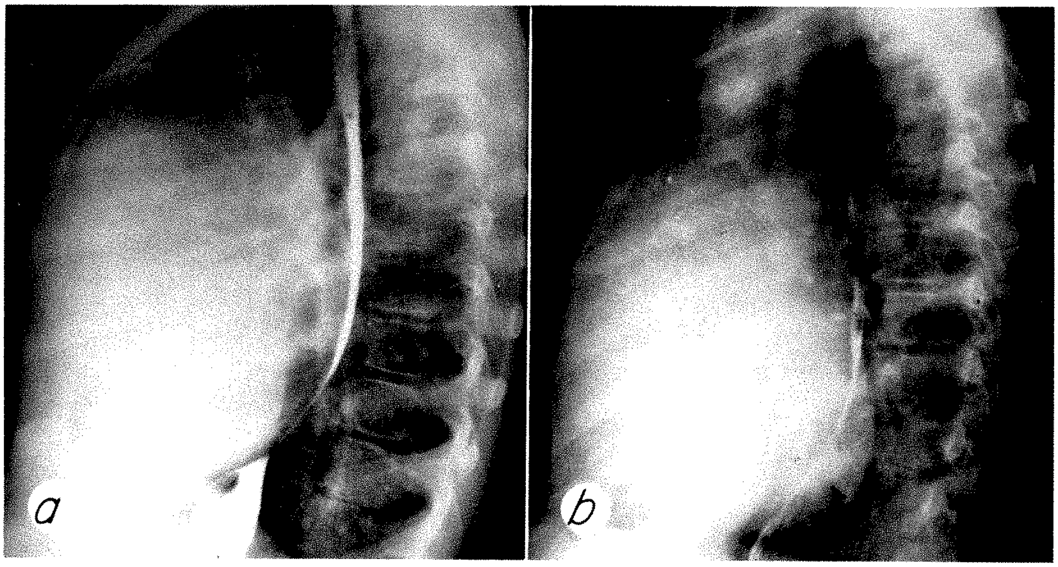

Fig. 6. Thoracic roentgenograms in same case as Figure 5*a*. Thirteen year old girl. (*a*) Lateral projection showing vertical convexity of the sternum owing to considerable enlargement of right side of heart. There is left atrial enlargement, as well. (*b*). Left anterior oblique view. Oblique downward bulge of the posterior portion of the heart (arrow) beyond the barium-filled esophagus, indicating left ventricular enlargement.

in the left anterior oblique projection in only 3 cases as evidenced by projection of the posterior cardiac border beyond the barium-filled esophagus (Fig. 6*b*). In the remaining 11 cases, it appeared that the enlarged right side of the heart was pushing backwards the normally sized left ventricle (Fig. 7*b*). In these cases, the posterior border of the left ventricle was displaced directly posteriorly. The difficulty, however, of objectively judging left ventricular enlargement in the presence of right ven-

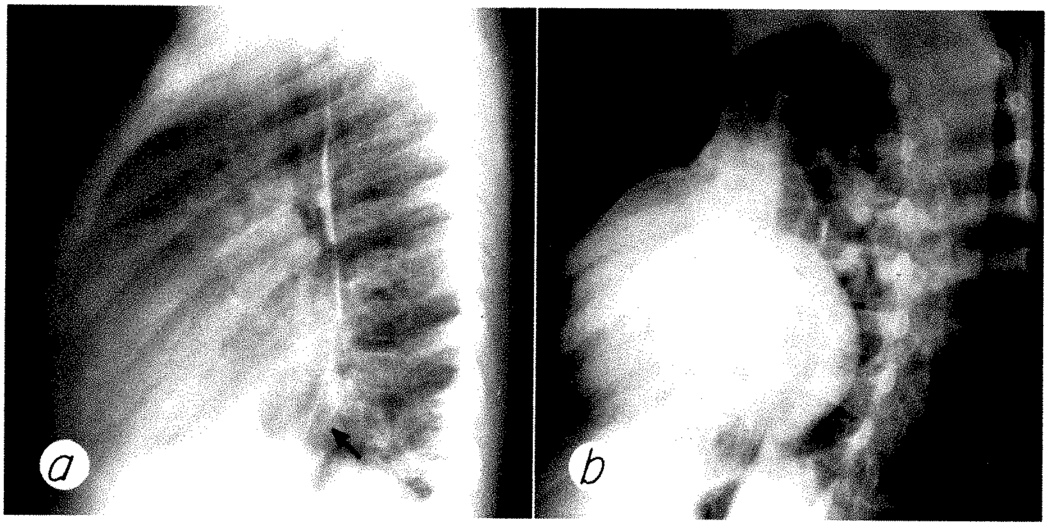

Fig. 7. (*a*) Lateral thoracic roentgenogram in same patient in as Figure 4*f*. There is considerable right-sided cardiac enlargement coexisting with left atrial and left ventricular enlargement (arrow). (*b*) Seventeen year old boy. Left anterior oblique projection in same patient as Figure 4*e* showing signs consistent with an enlarged right side of heart pushing posteriorly the normal-sized left ventricle. Electrocardiographically, the left ventricle was enlarged.

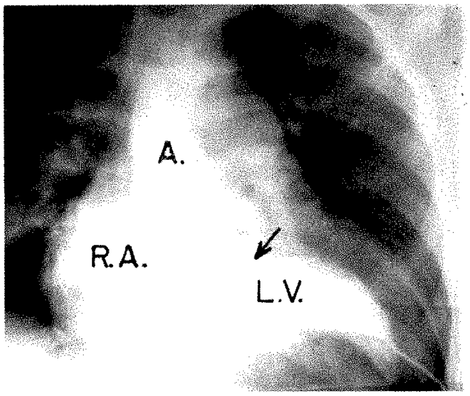

FIG. 8. Thirteen year old girl studied at necropsy. Selective ventriculography by means of a percutaneous transthoracic insertion of the catheter into the left ventricle.[17] Frontal projection shows anatomic definition of the left ventricle (L.V.) and the right atrium (R.A.) as well as of the ascending aorta (A.). In addition to the LV-RA communication, there is subaortic stenosis (arrow). Retrograde aortography gave negative results.

tricular enlargement cannot be overemphasized.

It is noteworthy that signs of mild left atrial enlargement may occur in adult patients with atrial septal defect. The importance of this will be discussed in the *Comment.*

The right anterior oblique projection showed dilatation of the pulmonary trunk and mild to moderate degrees of left atrial enlargement.

CHANGES WITH AGING

Successive studies were available in 10 of the 14 subjects. With increasing age, each patient studied showed signs of progressive enlargement of the right side of the heart. Yet, the over-all configuration of the heart remained enlarged and globular and signs of left-sided cardiac enlargement persisted (Fig. 5 *a* and Fig. 6, *a* and *b*). Moreover, the pulmonary trunk, its branches in the hilus, and the distal pulmonary vessels remained dilated, a situation which indicates increased blood volume in the pulmonary circulation.

In 4 of these patients, the heart developed a "ball-shaped" contour, shown best in either the left anterior oblique or right anterior oblique projections. This seemed to be the result of severe right atrial and right ventricular enlargement coexisting with left-sided enlargement.

ANGIOCARDIOGRAPHIC FINDINGS

Selective angiocardiography from the left ventricle was performed in 3 subjects, each admitted for study within the last 3 years.

Peripheral and selective injections of contrast material into the right ventricle had been performed in 4 other patients, but these techniques were not helpful in establishing the diagnosis.

In each of the 3 cases in which selective angiocardiography from the left ventricle was performed, a diagnosis of LV-RA communication was established by this method (Fig. 8). Injection of contrast material resulted in immediate opacification and anatomic definition of the left ventricle, followed in very short order by opacification and anatomic definition of the right atrium. In the patient whose angiocardiogram is shown in Figure 8, subaortic stenosis was additionally present.

In each of the 3 cases, selective aortography excluded rupture of an aortic sinus aneurysm into the right atrium.

COMMENT

For optimal surgical results in patients with an abnormal communication between the cardiac chambers, it is desirable to know the precise site of entry and exit of the communication.

The condition reported here, LV-RA communication, is uncommon as judged by relatively few reports on this subject[1,2,5,6,7,11,12,14,15,17] and by the fact that, in our material, numbering over 800 pathologic specimens with congenital cardiac disease, there are only 4 examples of this condition without associated transposition of the great vessels. The clinical and hemodynamic findings, in some respects, are like those in more common forms of intracardiac communication; namely, atrial septal defect, ventricular septal defect, and certain defects of the atrioventricular commune type. As a result, certain cases of LV-RA communication in the past have first been diagnosed at time of operation. For these reasons, once a left-to-right intracardiac shunt has been suspected by the roentgenologist, the presence of LV-RA communication should always be considered. Moreover, the relatively complicated surgical approach necessary in the condition under consideration emphasizes the importance of its differentiation from the usual case of ventricular septal defect.

In a study of the roentgenograms, there were certain findings which, when analyzed in a retrospective manner, yielded signs highly suggestive for LV-RA communication.

In the frontal projection, the over-all roentgenologic picture seemed, in our opinion, to simulate most closely that in atrial septal defect. The features were the small size of the aorta, the extremely prominent pulmonary vascularity and the associated cardiomegaly. Yet, among the majority of patients, there were certain roentgenologic findings in the other projections which were unusual for an uncomplicated atrial septal defect.

The most striking feature was the paradoxical situation of extreme degrees of right-sided cardiac enlargement associated with coexistent evidence of left-sided enlargement.

It should be remembered that adult patients with atrial septal defects not uncommonly show signs of mild left atrial enlargement, a feature that may represent the most difficult problem in differentiating atrial septal defect from LV-RA communication by roentgenography. Demonstration of an enlarged left ventricle is the most important finding which favors a diagnosis of LV-RA communication over atrial septal defect.

In the cases reported here, in which left ventricular enlargement was not demonstrable roentgenologically, other clinical studies, such as electrocardiography, played an important role. As mentioned earlier, the majority of patients showed electrocardiographic evidence of biventricular enlargement, a feature which does not occur in uncomplicated atrial septal defect.

The method of choice in establishing the diagnosis of LV-RA communication is selective left ventriculography. In each of the 3 cases studied by this technique, there was opacification and anatomic definition of the left ventricle, followed immediately by opacification and anatomic definition of the right atrium. This precise sequence of events can occur only in this condition.

There are, however, two uncommon conditions which may present considerable difficulty in differential diagnosis if additional angiocardiographic studies are not performed. These are rupture of an aortic sinus aneurysm into the right atrium, and ventricular septal defect coexisting with insufficiency of the tricuspid valve.

Selective aortography is the procedure of choice in the demonstration of rupture of an aortic sinus aneurysm into the right atrium. It is the opinion of the authors that aortography should be performed in all patients in whom either LV-RA communication or ruptured aortic sinus aneurysm is suspected. In the cases of LV-RA communication herein reported, selective aortography showed an intact aortic valve and aorta, whereas in rupture of an aortic sinus aneurysm into the right atrium selective aortography shows immediate opacification of the right atrium.

When a ventricular septal defect coexists with tricuspid insufficiency, selective left ventriculography may give results which may be confused with anatomic LV-RA communication. If the problem is an incompetent tricuspid valve, right ventriculography will readily demonstrate it.

It is of interest that LV-RA communication may also be observed in cyanotic forms of congenital cardiac disease. The authors recently reported LV-RA communication occurring in 3 cases of complete transposition of the great vessels.[4]

SUMMARY

The roentgenologic findings were studied in 14 cases of left ventricular-right atrial communication. Pathologic data were available in 4 of the cases.

The condition, left ventricular-right atrial communication, was indistinguishable from other and more common forms of congenital cardiac septal defect without cyanosis on the basis of clinical, electrocardiographic, and hemodynamic findings.

Roentgenographic studies may yield results suggestive of this condition. The essential features were considerable right atrial dilatation coexisting with signs of left-sided cardiac enlargement. Selective left ventriculography, done in 3 of the cases, was the only means of establishing the correct anatomic diagnosis, clinically.

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VOL. 93, NO. 2

ANGIOCARDIOGRAPHIC FINDINGS IN IDIOPATHIC MYOCARDIAL HYPERTROPHY WITH RIGHT AND LEFT VENTRICULAR OUTFLOW TRACT OBSTRUCTION*

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IDIOPATHIC myocardial hypertrophy has been most commonly discovered during the second and third decades of a patient's life, the diagnosis having been made only rarely during infancy. In this cardiac abnormality, hypertrophy of the left ventricular wall and the ventricular septum often results in a variable degree of subaortic stenosis. There is usually some degree of hypertrophy involving the right ventricle also, but to a lesser extent. Involvement of the ventricular septum may occasionally be sufficiently marked as to lead to outflow tract obstruction of both the left and right ventricles. Evidence of combined subaortic and pulmonary infundibular obstruction, in several of the cases of hypertrophic obstructive cardiomyopathy reported recently by Cohen and associates,[1] suggests that this may not uncommonly occur. Although the predominant findings are usually those of subaortic stenosis, idiopathic myocardial hypertrophy may rarely present itself as severe pulmonary stenosis, masking the left ventricular component.[3]

It is the purpose of this presentation to report the roentgenographic findings in such a case of idiopathic myocardial hypertrophy in a 3 week old infant. The angiocardiographic features in this case suggest that a correct roentgenologic diagnosis of this rare condition may be made.

REPORT OF A CASE

Clinical and Roentgenologic Findings. The patient, a female infant, was the product of a full term pregnancy. The mother had been taking diuretics for swelling of the hands, but there had been no other evidence of toxemia. At birth, the patient's weight was 7 pounds and 15 ounces. Unusual drowsiness and grunting respirations were recorded at the time of birth. At the age of 12 hours, slight cyanosis and a cardiac murmur were recorded. Throughout the following days, the patient's condition appeared to be improving, but the oral intake remained poor and there were episodes of mild cyanosis with feedings. The patient was discharged from the hospital at 1 week of age.

The symptoms persisted and she was admitted to the University of Minnesota Hospitals for further evaluation.

Physical examination at the age of 3 weeks revealed a slightly cyanotic, white female infant. The clinically significant cardiac findings were cardiomegaly and a moderately loud, long systolic murmur along the left sternal border which extended into early diastole. There were no palpable thrills. Electrocardiographic examination demonstrated marked right axis deviation, right ventricular hypertrophy, right atrial enlargement, questionable left atrial enlargement and first degree heart block. A QRS vectorcardiogram was interpreted as showing right ventricular hypertrophy. The results of right-sided cardiac catheterization at the age of 3 weeks showed the presence of a right-to-left shunt at the atrial level and a right ventricular systolic pressure of 125 to 130 mm. Hg.

Roentgenograms of the thorax demonstrated marked cardiomegaly and normal pulmonary vascularity (Fig. 1, *A* and *B*). Selective angiocardiograms made from the right ventricle (Fig. 2, *A* and *B*; 3, *A* and B; and 4, *A* and *B*) showed a small right ventricular cavity and a markedly hypertrophied right ventricular wall

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and ventricular septum, the latter causing a large filling defect in the right ventricular chamber. The pulmonary valve was somewhat thickened but there was no other definite evidence of pulmonary valvular stenosis. The main pulmonary artery was enlarged. A cine-angiocardiogram was performed by injecting contrast material into the right ventricle. The results of this examination were interpreted as showing "doming" of the pulmonary valve. On the basis of the markedly elevated right ventricular pressure and the "doming" of the pulmonary valve, an erroneous diagnosis of pulmonary valvular stenosis was made. The patient was referred to the surgical service and pulmonary valvulotomy was attempted, the approach to the valve being made through the pulmonary trunk. Due to postoperative complications, the patient expired on the nineteenth day following operation.

Pathologic Findings. At necropsy, the significant cardiovascular findings included purulent pericarditis and hypertrophy of the left and right ventricular walls which measured 10 mm. and 8 mm. in thickness, respectively. The ventricular septum was intact and was so severely hypertrophied that it bulged into the outflow tracts of both ventricles, resulting in muscular subaortic stenosis (Fig. 5*A*) and muscular right ventricular infundibular stenosis (Fig. 5*B*). Less significant findings included slight endocardial thickening in the subaortic area of the left ventricle. Only one papillary muscle was present in the left ventricle. This was attached to the anteroseptal wall near the apex. The chordae tendineae of both the anterior and the posterior leaflets of the mitral valve converged towards the solitary papillary muscle, giving the mitral valve the characteristic appearance of the "parachute mitral valve."[5] The walls of both atria were hypertrophied.

COMMENT

Idiopathic myocardial hypertrophy, also referred to as obstructive cardiac myopathy, muscular subaortic stenosis or asymmetric hypertrophy of the heart, is a well recognized clinical and pathologic entity. In some cases, there has been a definite familial incidence, leading to such terms as idiopathic familial cardiomegaly.[2,4,7] Marked hypertrophy of the left ventricular wall and some hypertrophy of the right ventricular wall are usual findings. There is also a variable degree of hypertrophy of the ventricular septum resulting in left ventricular outflow tract obstruction. Less often, the ventricular septum becomes so markedly hypertrophied that it bulges into the outflow tract of the right ventricle, as well as that of the left ventricle. This may lead to right ventricular infundibular stenosis, as well as subaortic obstruction. In this condition, the infundibular obstruction may become the dominant clinical finding, masking the left-sided obstructive component[3] as evidenced by this case.

The findings on thoracic roentgenograms of this patient (Fig. 1, *A* and *B*) were nonspecific cardiomegaly, without significant left atrial enlargement, and a normal pulmonary vasculature. Forward angiocardiography and selective right ventriculography demonstrated marked right ventricular hypertrophy with a huge filling defect impinging upon the right ventricular cavity, apparently due to the massively enlarged ventricular septum. During systole (Fig. 2, *A* and *B*), the right ventricular outflow tract appeared almost completely pinched off and there was a jet of contrast material, apparently originating from the narrowed segment of the outflow tract rather than from the pulmonary valve. This finding is consistent with infundibular obstruction in view of the absence of doming of the pulmonary valve. During diastole (Fig. 3, *A* and *B*), however, the right ventricular outflow tract appeared completely dilated. This should have indicated that the obstruction was not a fibrous type of infundibular obstruction, such as may be seen in tetralogy of Fallot, but, rather, was an obstruction produced by muscular hypertrophy.

Unfortunately, the left-sided outflow tract obstruction was not visualized on our study, since selective left ventriculography was not performed. In the levogram phase of the forward angiocardiogram, however, there was noted an unusual configuration of the left ventricular cavity which was probably a manifestation of the muscular hypertrophy (Fig. 4, *A* and *B*). There was, furthermore, angiocardiographic evidence

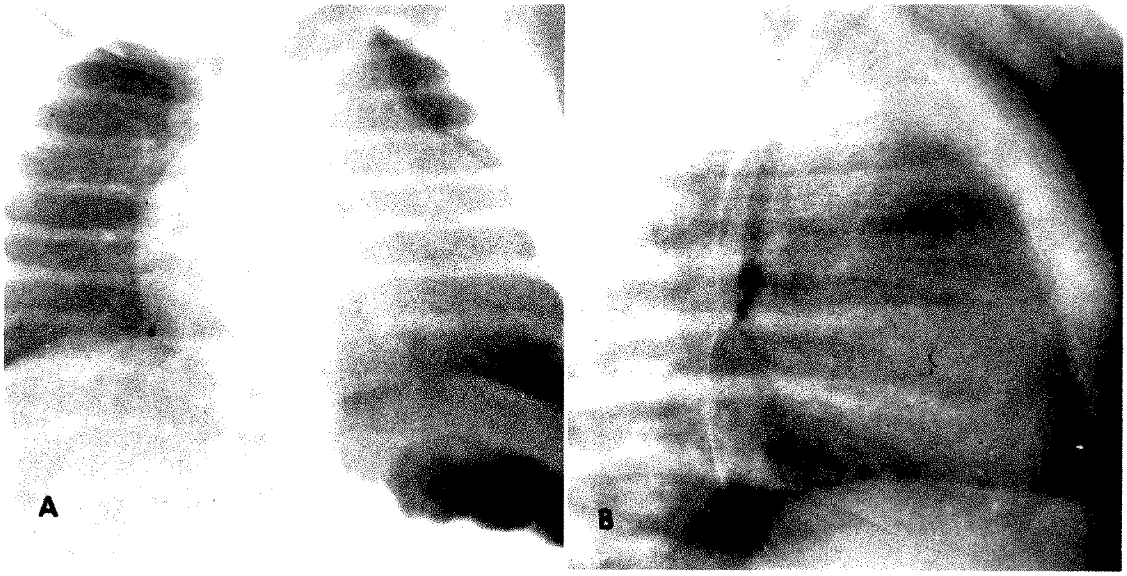

Fig. 1. (*A*) Posteroanterior and (*B*) lateral roentgenograms of the thorax. There is marked cardiomegaly and a normal pulmonary vasculature. There is no significant degree of left atrial enlargement on the lateral roentgenogram.

of enlargement of the left atrium.

In typical cases of idiopathic myocardial hypertrophy, selective left ventriculography shows a heavily trabeculated, thick-walled left ventricle. During systole, there is usually marked narrowing of the left ventricular outflow tract which disappears during diastole. A bulging, hypertrophied septum can be seen impinging on the left ventricular outflow tract. Since this type of muscular left or right ventricular outflow tract obstruction cannot be adequately assessed hemodynamically by angiocardiography, pressure measurements are of para-

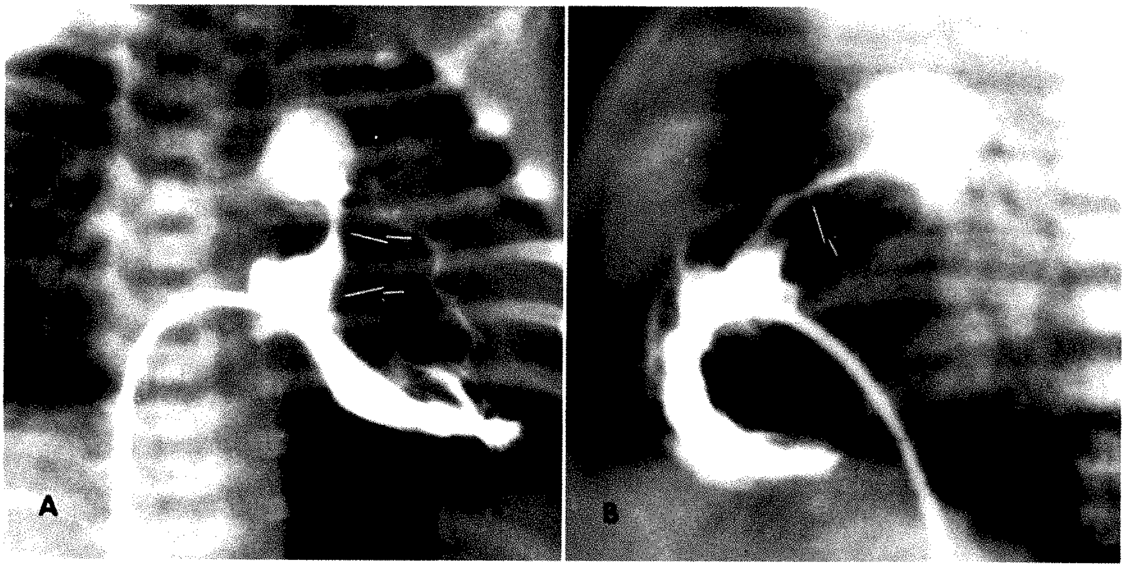

Fig. 2. (*A*) Anteroposterior and (*B*) lateral roentgenograms obtained on selective right ventricular angiocardiography during systole. There is a large filling defect (arrows) due to bulging of the septum into the right ventricular cavity. The jet phenomenon (arrow) on the lateral roentgenogram appears to be originating from the outflow tract of the right ventricle. There is no doming of the pulmonary valve.

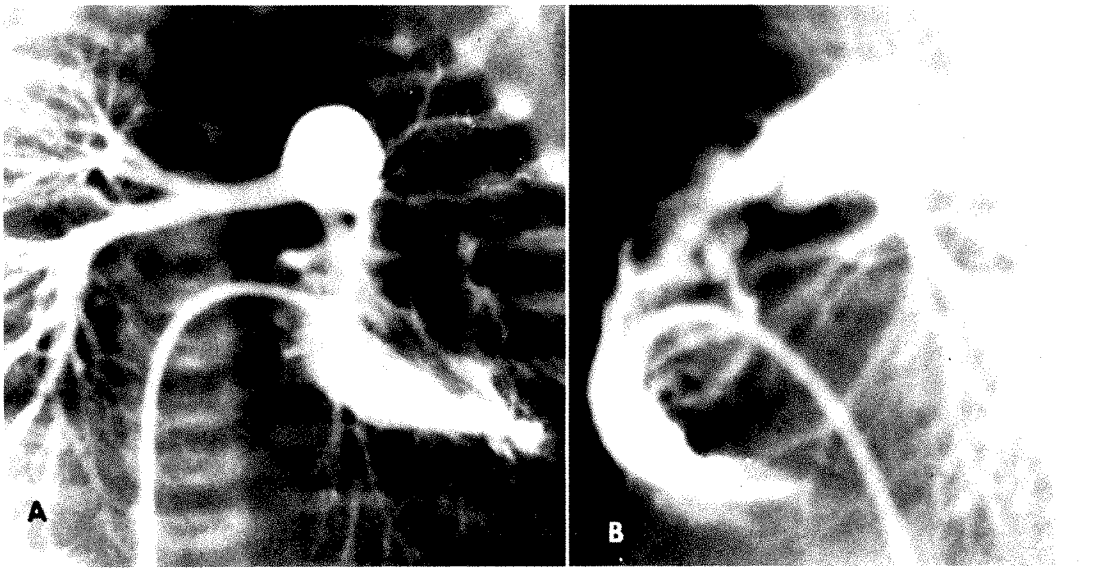

FIG. 3. (*A*) Anteroposterior and (*B*) lateral views obtained on selective right ventricular angiocardiography during diastole. There is dilatation of the right ventricular outflow tract. The main pulmonary artery is enlarged. The left pulmonary artery is unusually small, as may be seen in many other congenital cardiac lesions.

mount importance. In some cases of idiopathic myocardial hypertrophy, there is no significant subaortic systolic pressure gradient. This suggests that, in these cases, muscular hypertrophy is the primary event and that when right or left ventricular outflow tract obstruction occurs, the latter is secondary to the massive myocardial hypertrophy. The work of Whalen and associates[6] suggests that a systolic pressure gradient may be elicited in such cases by exercise or by the administration of isoproterenol.

SUMMARY AND CONCLUSIONS

Idiopathic myocardial hypertrophy is a well recognized entity most commonly in-

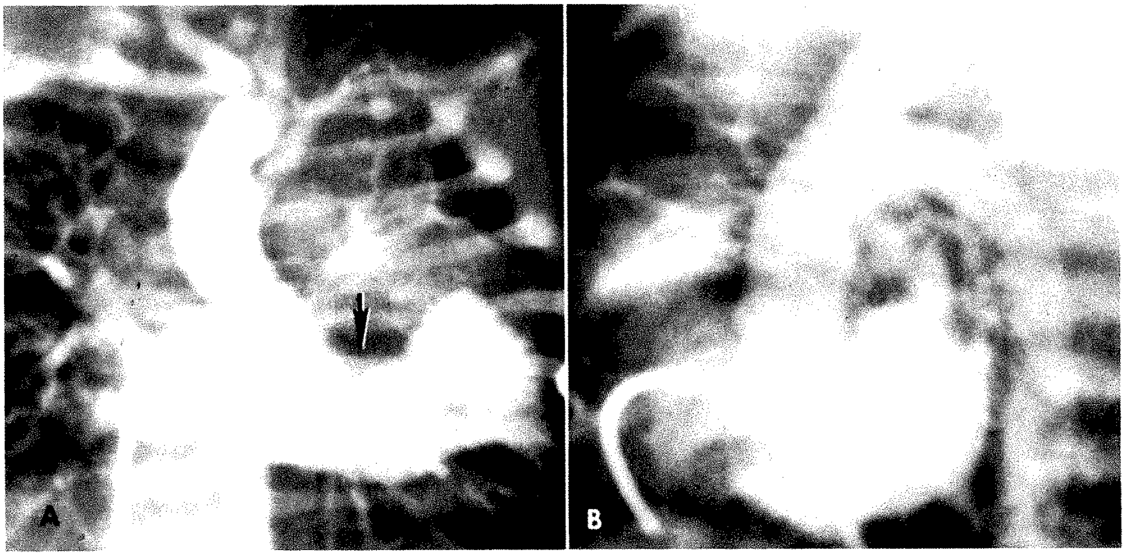

FIG. 4. (*A*) Anteroposterior and (*B*) lateral views obtained on the levogram phase of a forward angiocardiographic study. There is an unusual configuration of the left ventricular cavity, as may be seen in idiopathic myocardial hypertrophy. There is slight left atrial enlargement.

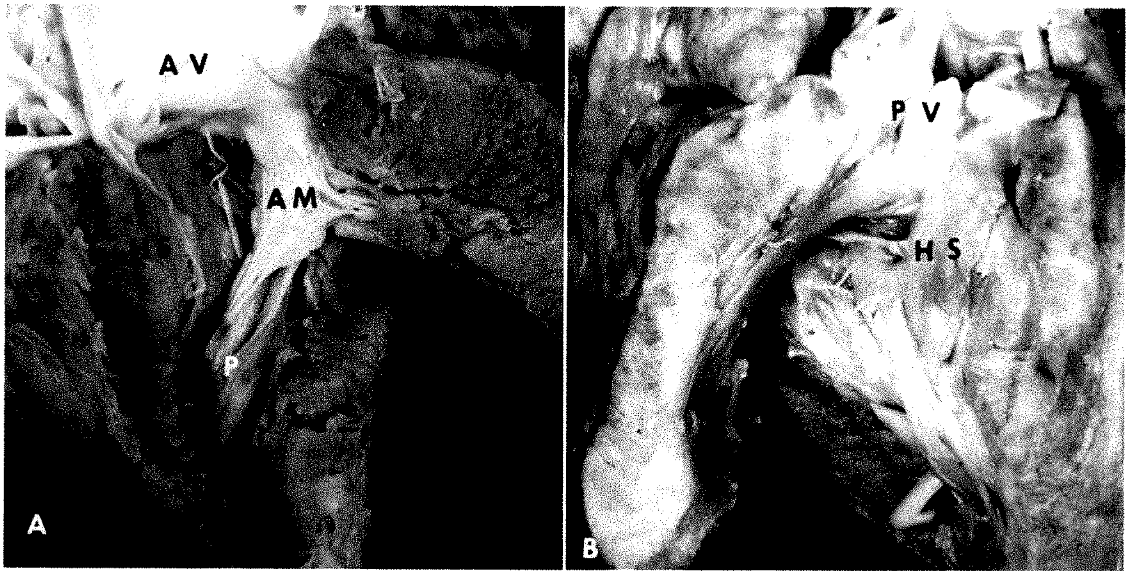

Fig. 5. (*A*) Interior of left ventricle and opened aortic valve (AV). (*B*) Interior of right ventricle and opened pulmonary valve (PV). The free walls of both ventricles and the ventricular septum are hypertrophied. The hypertrophied septum (HS) bulges into the outflow tract of both ventricles. In the other ventricular cavity, the solitary papillary muscle (P) has been incised. The anterior mitral leaflet (AM) hides most of the posterior leaflet.

volving the ventricular septum and the left ventricular wall and usually resulting in a variable degree of left ventricular outflow tract obstruction. Less commonly, there may be marked involvement of the ventricular septum, leading to significant right ventricular outflow tract obstruction as well. This was the dominant clinical feature in the presented case, masking the coexistent subaortic obstruction. Features of right and left selective ventriculography are massive thickening of the ventricular walls and the ventricular septum with narrowing of the outflow tracts during systole, but with disappearance of this narrowing on diastole. The presence of a jet originating in the region of the right ventricular outflow tract, without doming of the pulmonary valve, together with marked thickening of the ventricular septum and left ventricular wall, is highly suggestive of idiopathic myocardial hypertrophy with outflow tract stenosis of both ventricles.

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ANOMALOUS ORIGIN OF THE LEFT CORONARY ARTERY FROM THE PULMONARY ARTERY*

ANGIOGRAPHIC AND PATHOLOGIC STUDY OF A CASE

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THE roentgenographic diagnosis of anomalous origin of the left coronary artery from the pulmonary artery is made by coronary arteriography. Intravenous angiocardiography supplements the diagnosis. Because of the surgical implications, many reports have recently appeared in the literature.[2,3,10,12,14,16,24] The degree of collateral circulation and the direction of blood flow through the left coronary artery are useful criteria for selection of patients for ligation of the vessel. Although the presence of predominant left-to-right blood flow through extensive collaterals was in favor of surgical intervention in the case herein described, ligation of only one branch of the left coronary artery proved fatal. Correlation of the angiographic and pathologic findings of this case form the basis of this report.

REPORT OF A CASE

A 4 month old white female infant was admitted on July 8, 1963, with a history of failure to gain weight, dyspnea, tachypnea, cough, and hyperpnea. The child was the second born to a 20 year old mother after a normal, full-term, spontaneous delivery that followed an uncomplicated pregnancy. She weighed 8 pounds, 1 ounce at birth and was mentally alert. Within the first few weeks of life, the child began to feed poorly and show hyperhidrosis, dyspnea, and cough. At 3 months she was admitted to another hospital in heart failure, but the etiology was not established. On the date of discharge July 2, 1963, she was not improved and was referred to this hospital.

On admission, she was well-developed but thin, and in distress. A soft, high-pitched systolic murmur (Grade 2) was heard along the lower left sternal border in the fourth interspace; this radiated to the apex and axilla. S_2 on the left was greater than S_2 on the right and was closely split. The liver was palpated 4 cm. below the right costal margin and the spleen was felt 1 cm. below the left costal margin. Serial electrocardiograms showed changes consistent with an intraventricular conduction defect and myocardial ischemia. Roentgenograms of the chest revealed marked cardiomegaly, obstructive emphysema of the right middle lobe, and partial collapse of the right upper lobe (Fig. 1, *A*, *B* and *C*). Intravenous angiocardiography and cineangiocardiography were performed on July 12, 1963, and revealed a large, pulsatile left atrium and a hugely dilated left ventricle (Fig. 2, *A* to *H*). Especially striking was the intravenous cineangiocardiogram which showed the contrast medium passing from the left atrium into the left ventricle in a cascade fashion. The left ventricle contracted poorly and remained opacified for a prolonged period. The right atrium and ventricle were small and appeared displaced superiorly and anteriorly (Fig. 2, *A* and *B*). A small segment of the left coronary artery was visualized arising from the pulmonary artery (Fig. 2, *C*, *D*, *E* and *F*). Retrograde aortography was performed the next day and showed the right coronary artery to arise in the normal position. The proximal portion of this vessel was dilated. The dilated portion divided into numerous ramifications which anastomosed with the branches of the left coronary artery; these filled in a retrograde fashion and emptied into the pulmonary artery (Fig. 3, *A* to *F*). On July 31, 1963, the patient underwent a surgical procedure for ligation of the left coronary artery. During the

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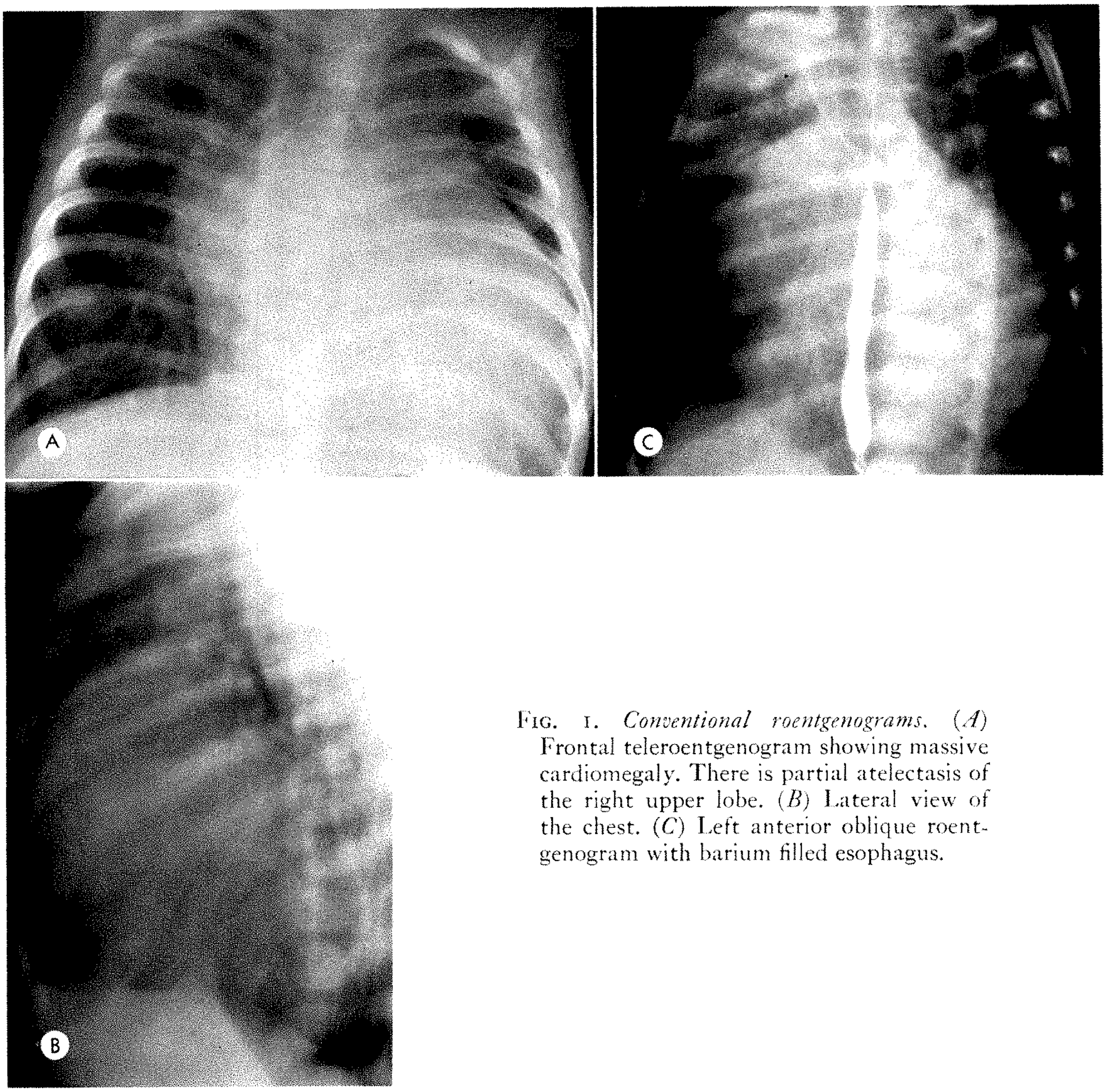


Fig. 1. *Conventional roentgenograms.* (*A*) Frontal teleroentgenogram showing massive cardiomegaly. There is partial atelectasis of the right upper lobe. (*B*) Lateral view of the chest. (*C*) Left anterior oblique roentgenogram with barium filled esophagus.

operation and immediately after ligation of the vessel, no electrocardiographic abnormalities were observed; however, when the patient reached the recovery room, the normal sinus rhythm became nodal and within 10 minutes cardiac arrest ensued. Despite all resuscitative measures, she succumbed.

NECROPSY FINDINGS

The body was that of a well-developed female infant, weighing 4.1 kg. and measuring 60 cm. in length. The principal findings were limited to the heart. The heart and lungs together weighed 162 gm. (expected weight 97 gm.). The heart was massively enlarged and occupied two-thirds of the thoracic cavity (Fig. 4*A*). The right border of the heart was formed by the left atrium superiorly and the left ventricle inferiorly (Fig. 4*B*). The anterior surface of the heart was formed, from right to left, by the wall of the left ventricle, the wall of the right ventricle, and the left ventricle (Fig. 4*C*). The venae cavae and pulmonary veins were normal (Fig. 4*A*). The tricuspid valve and right atrium were normal in size. The enlarged left ventricle virtually surrounded the normal-sized right ventricle on three sides. The latter was displaced cephalad and to the left and formed the mid-portion

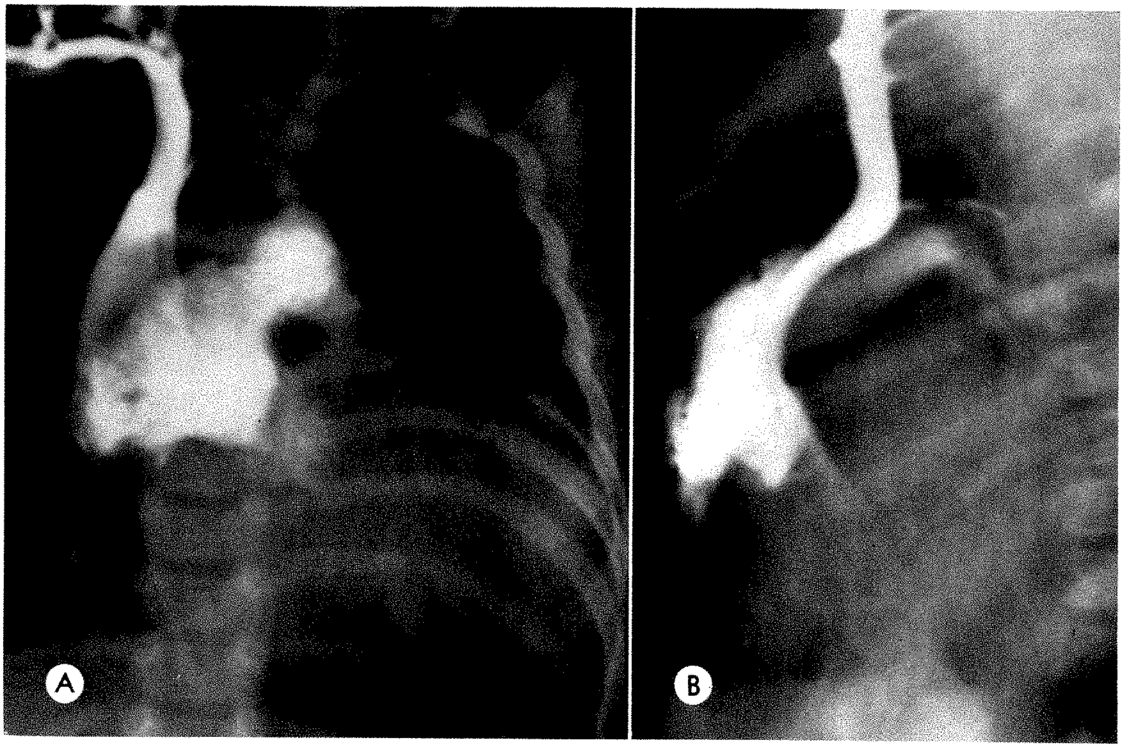


FIG. 2. *Intravenous angiocardiograms.* (*A*) The right atrium and ventricle are displaced anteriorly, superiorly, and towards the right hemithorax. (*B*) Biplane of (*A*).

of the anterior surface of the heart (Fig. 4*C*). The wall of the right ventricle at the base and at the apex measured 3 mm. in thickness. The endocardium of the markedly enlarged left atrium was yellow-white, opaque and thickened by proliferated elastic and collagen fibers that covered markedly hypertrophied myofibers. The circumference of the mitral valve ring was 5.2 cm.; the anterior leaflet of the mitral valve was retracted and thickened. The left ventricular chamber was voluminous and the thickness of the wall was 6 mm. at the base, 8 mm. in the mid-portion, and 3 mm. at the apex (Fig. 4*E*). The endocardium of the left ventricle was yellow-white, opaque and measured up to 2.5 mm. in thickness; it was continuous with bands of scar tissue that partially replaced the myocardium of the lateral wall, the interventricular septum, and that of the papillary muscles (Fig. 4*E*). Microscopically, sections of the free wall, apex, and base showed the scar tissue to be composed of bundles of proliferated collagen and elastic fibers that, in many areas, surrounded and embedded individual myofibers, especially in the inner one-third of the wall. In some places, the dense scar tissue totally replaced large areas of myocardium, whereas in others, the scar tissue was relatively more cellular and contained numerous fibroblasts, proliferated capillaries, and fragments of hypereosinophilic myofibers. There were focal areas of dystrophic calcification in the midst of the scar tissue. Where myofibers were intact, they were markedly enlarged and had bizarre-shaped, hyperchromatic nuclei. The anterior papillary muscle of the left ventricle was atrophic and pale, whereas the posterior papillary muscle was hypertrophied, and the myocardium was pink-red (Fig. 4*D*).

The ostium of the right coronary artery was in the wall of the aorta behind the right anterior cusp of the aortic valve. The ostium was widely patent, 2 mm. in diameter, and subserved the entire right coronary artery.

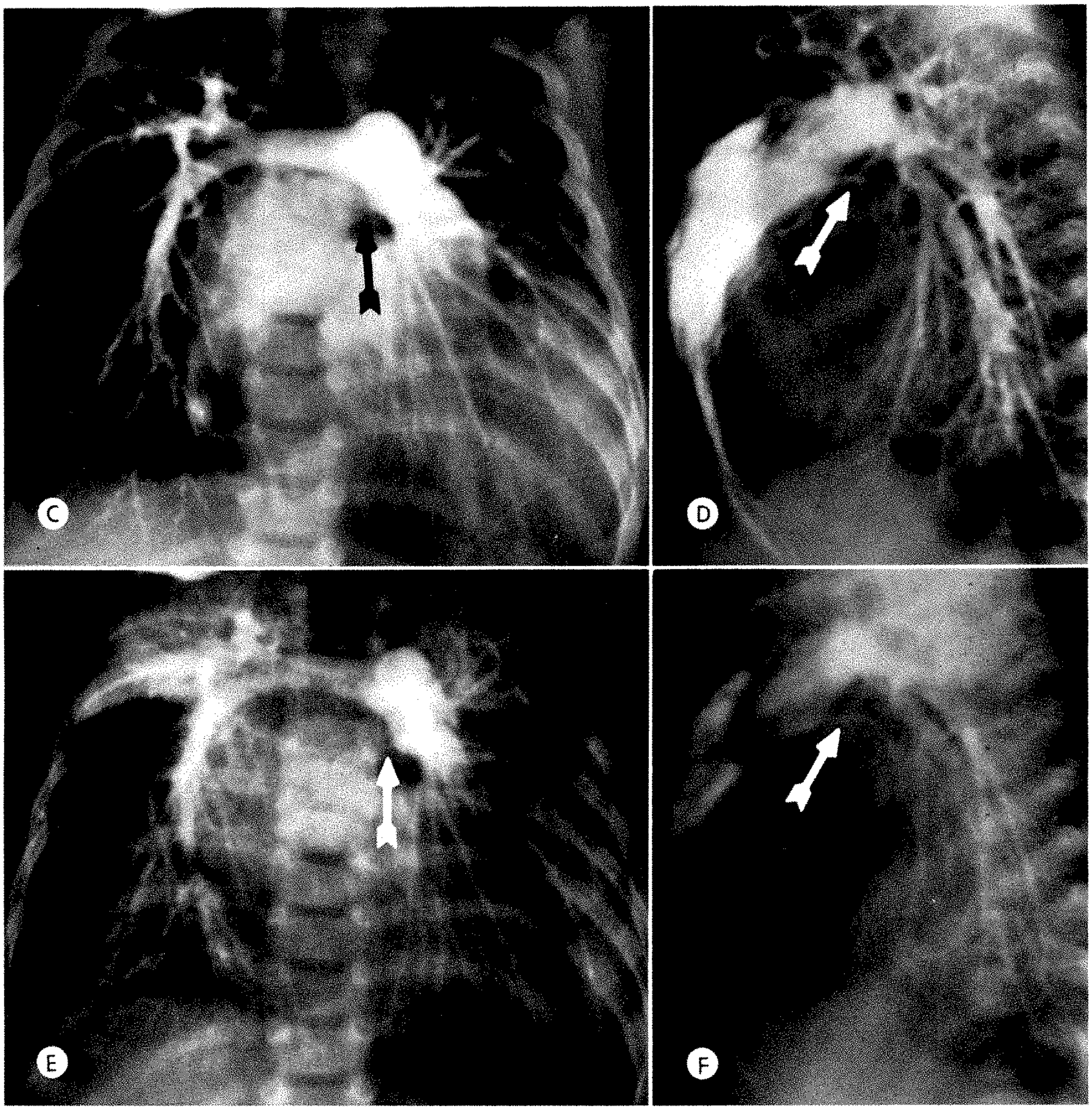


Fig. 2. (*C*) Serial angiocardiograms showing opacification of the anterior descending branch of the left coronary artery arising from the pulmonary artery (arrow). (*D*) Biplane of *C*; arrow points to circumflex branch of the left coronary artery. (*E*) Further filling of the anomalous left coronary artery (arrow). (*F*) Biplane of *E*.

The right coronary artery coursed to the right in the atrioventricular sulcus on the anterior wall. Two millimeters distal to its origin, it gave off a vessel that was 1.5 mm. in diameter, coursed to the left, descended on the left lateral aspect of the free wall of the right ventricle and ended by entering the anterior part of the interventricular septum. The sinus node artery originated 8 mm. distal to the ostium (Fig. 3*A*) and proceeded along the anterior wall of the right atrium beneath the right atrial appendage and terminated near the junction between the superior vena cava and the right atrium. Subsequently, the right coronary artery gave off branches at points 10 and 19 mm. distal to the origin that descended toward the apex on the anterior wall of the right ventricle and in the anterior interventricular sulcus (Fig. 3*B*). These de-

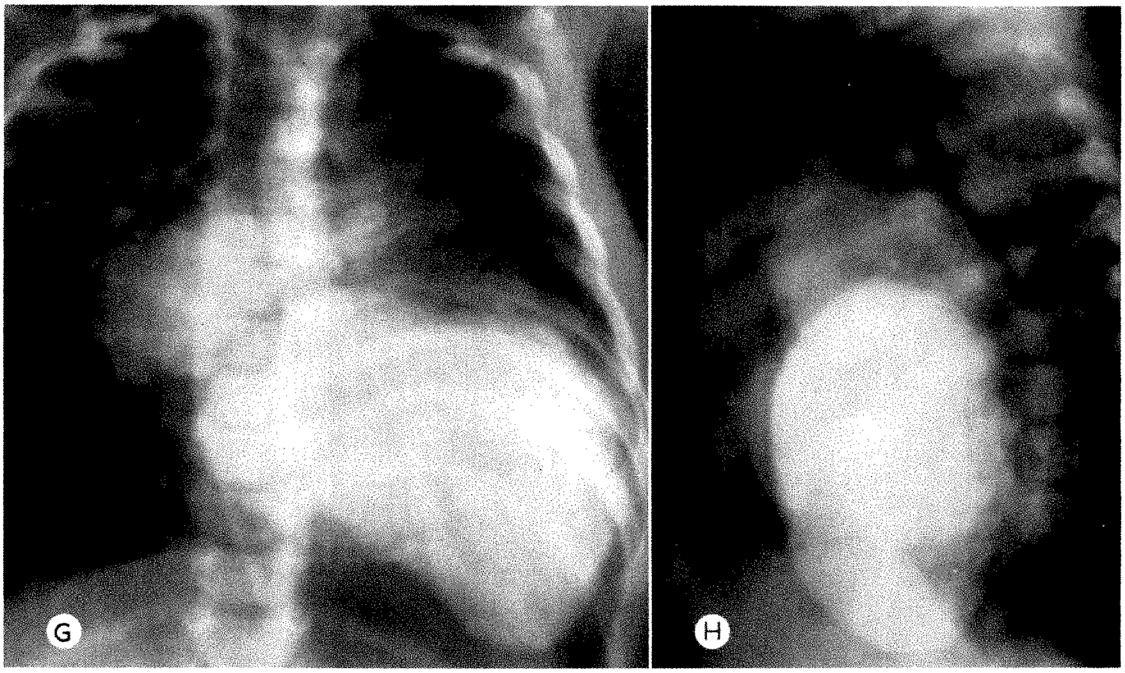


FIG. 2. (*G*) Angiocardiogram of the left heart structures showing the enlarged left atrium and ventricle. (*H*) Biplane of *G*.

scending branches supplied numerous large arteries that entered the myocardium of the interventricular septum and terminated in a spray of fine branches around the apex. The right coronary artery ended by dividing into numerous delicate arteries opposite the termini of the circumflex branch of the left coronary artery.

The left coronary artery originated from the posterior aspect of the pulmonary artery behind the left posterior cusp of the pulmonary valve (Fig. 4*F*). The ostium was 3 mm. in diameter, widely patent and subserved the entire left coronary artery. Two millimeters distal to the ostium, the main artery bifurcated into an anterior descending branch and a circumflex branch. The anterior descending branch coursed along the anterolateral border of the heart and on to the posterior wall in the interventricular sulcus. It was ligated by a single black silk suture 7 mm. distal to the bifurcation. Along the entire course numerous arteries, 1 mm. or less in diameter, originated at right angles from the main vessel and entered the myocardium of the interventricular septum. The artery terminated as many fine branches that anastomosed with termini or tributaries of the right coronary artery at the apex or on the inferior portion of the posterior surface of the heart. The circumflex branch of the left coronary artery coursed to the left in the atrioventricular sulcus and on to the posterior surface of the heart. At points 2, 12, 14 and 29 mm. distal to the bifurcation, branches took origin at right angles and descended on the lateral and posterior surfaces. They terminated by either dividing into several small superficial vessels that formed a plexus on the posterior wall or by continuing to the apex and there dividing into numerous small anastomotic vessels. The left circumflex artery terminated on the right border of the heart 35 mm. distal to the bifurcation. At this point it subdivided into numerous smaller branches; several of these branches ascended onto the anterior surface of the enlarged left atrium and the others anastomosed with termini of the right coronary artery at the base.

DISCUSSION

Anomalous origin of the left coronary

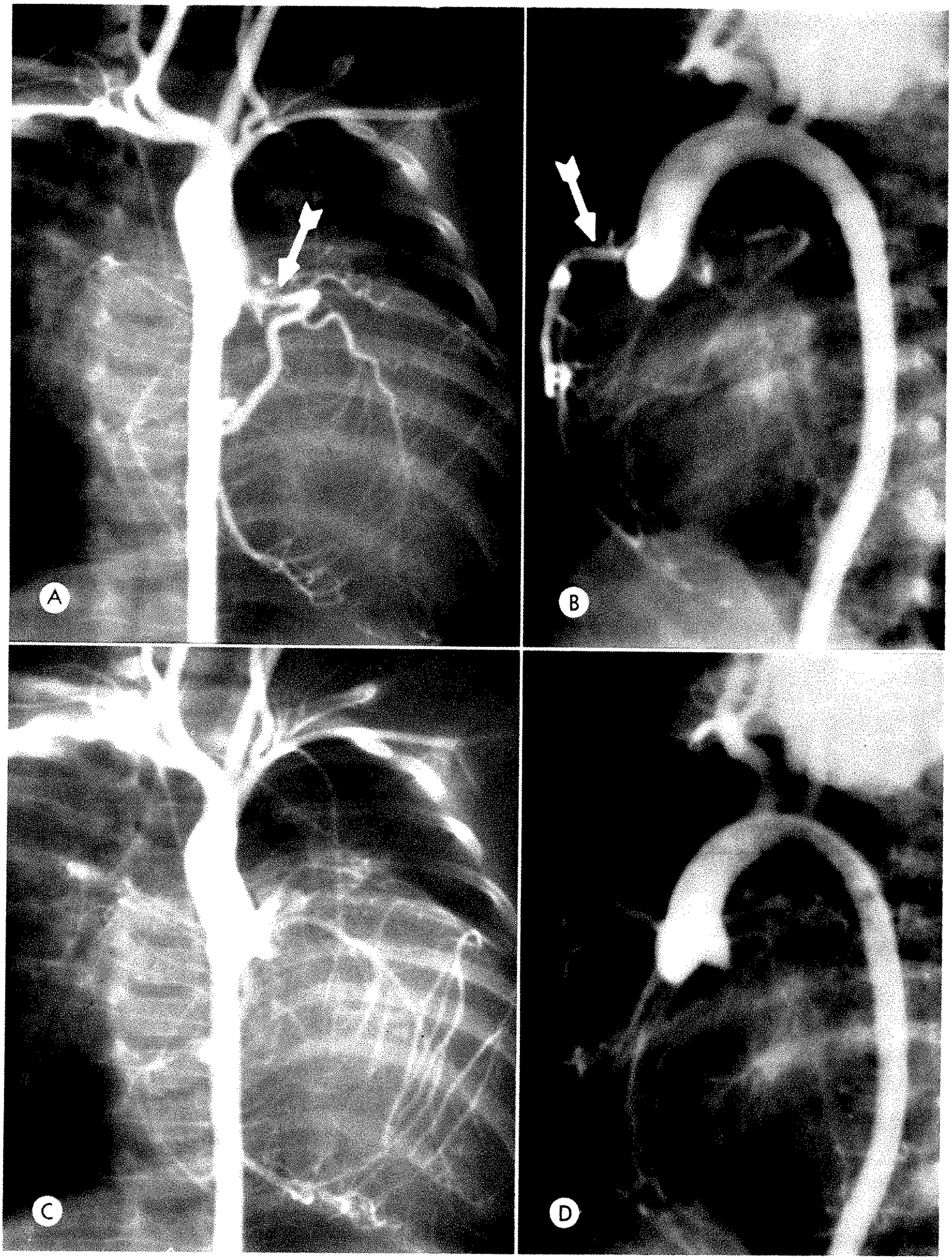


Fig. 3. *Selective aortograms.* (*A*) Frontal aortogram showing the enlarged right coronary artery (arrow). (*B*) Biplane of *A*; arrow indicates right coronary artery. (*C*) Later in the series, the anastomotic channels between the right and left coronary arteries were visualized. (*D*) Biplane of *C*.

artery from the pulmonary artery was classically described by Abrikossoff[1] in 1911. Bland, White and Garland[4] correlated the clinical and electrocardiographic features of the anomaly. Although the coronary arteries were first visualized in the experimental animal by Rousthöi[21] in 1933, it was not until 1952, following the review by Di Guglielmo and Guttadauro[7] of the retrograde aortography material of Lindgren, that visualization of the coronary arteries became practical in the human. Utilizing the techniques described by Seldinger[26] and, more recently, by Sones and Shirey,[27] coronary arteriography has become a well established procedure.

Two theories have been advanced to explain the embryology of the anomaly.[11,28] One is that the anlage of the left coronary artery arises *de novo* in the pulmonary artery; the other is that malrotation of the aorticopulmonary septum develops, so that the ostium of the left coronary artery eventually ends up on the pulmonary side of the truncus. It has been customary to classify the anomaly as infantile and adult types, according to whether the patient lives through infancy. Survival appears to be dependent upon the extent and efficacy of the collateral circulation. At birth, the physical examination usually shows a healthy infant, whereas several weeks to months later, dyspnea and tachypnea occur. Vomiting, colicky pain, sweating, pallor, and dyspnea are common, particularly during or immediately after feeding, and have been attributed to angina. Recurrent respiratory infections and congestive heart failure are not uncommon. The heart is enlarged and auscultation may reveal a systolic murmur of mitral insufficiency. Cyanosis of the lips and nail beds may occur. Electrocardiograms show ST segment elevation, inversion of T waves, left axis deviation, and bundle branch block. Cardiac catheterization may demonstrate an increase in oxygen saturation in the proximal portion of the main pulmonary artery when there is reversal of the flow in the anomalous coronary artery. This course of

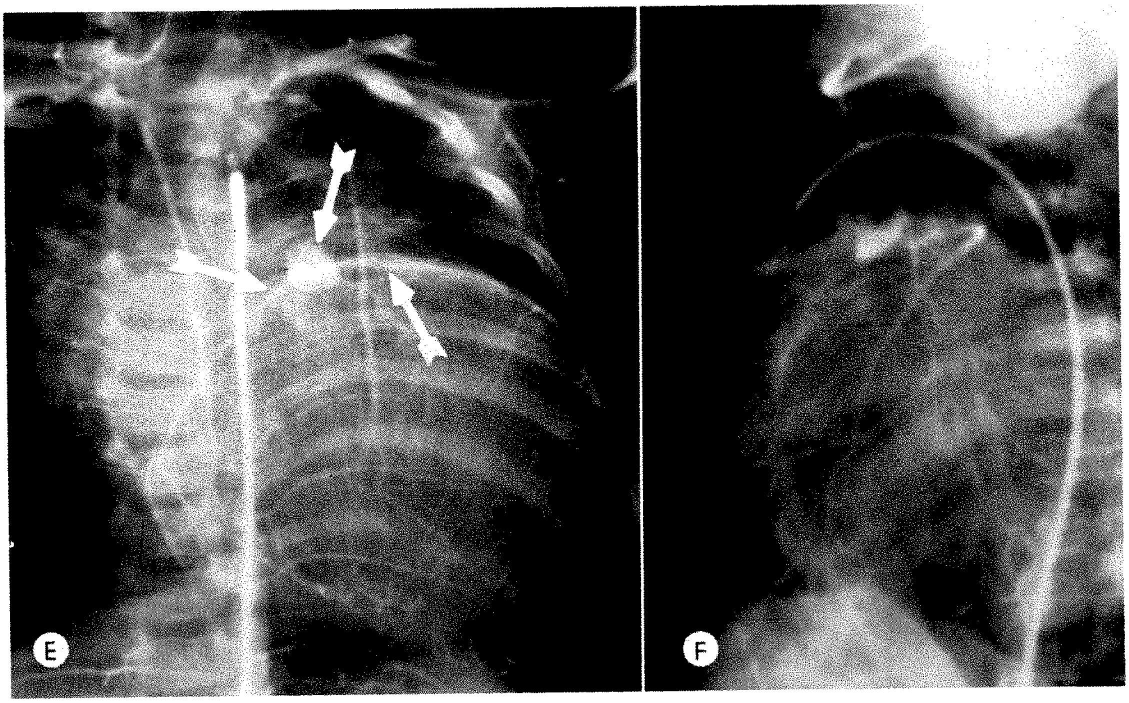


Fig. 3. (*E*) Frontal aortogram showing retrograde filling of the pulmonary artery (upper arrow); the lower arrows point to anterior descending and circumflex branches of the left coronary artery. (*F*) Biplane of *E*.

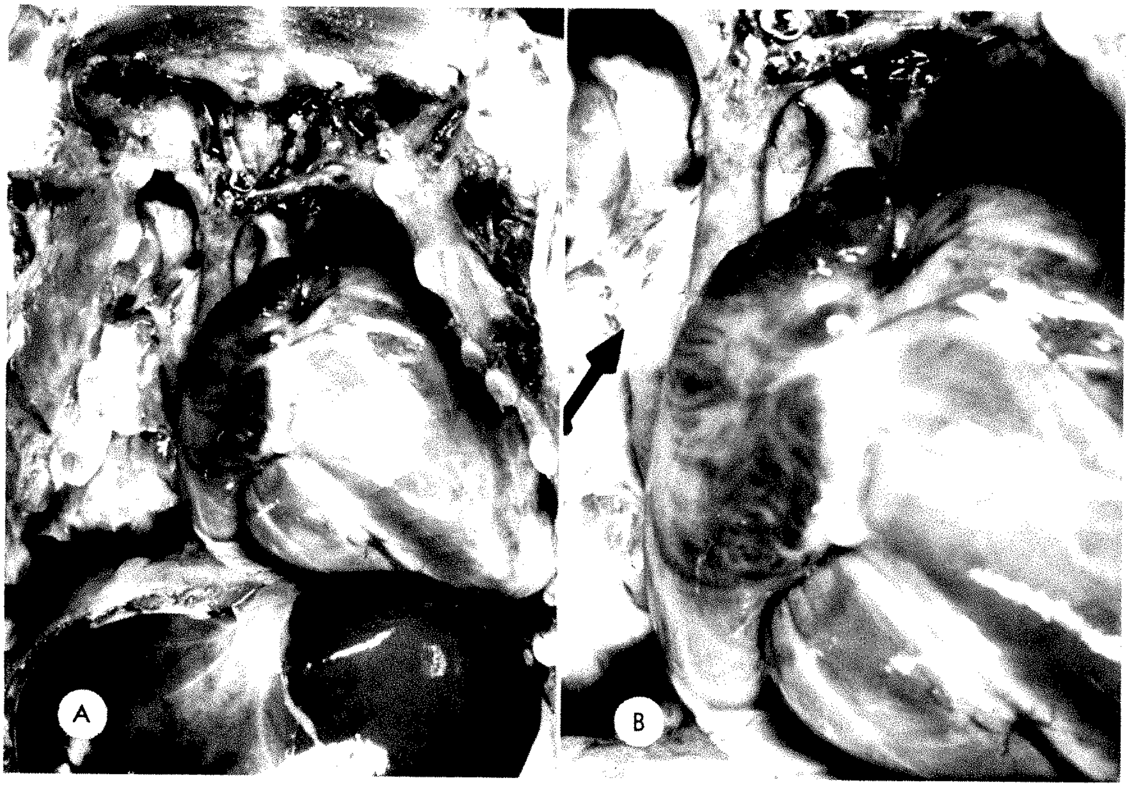


Fig. 4. *Photographs of the heart at necropsy.* (*A*) Heart *in situ* showing massive cardiomegaly. (*B*) Heart *in situ* showing the right border made up by the left atrium (arrow) and left ventricle (posterior to the inferior vena cava).

events was originally suggested by Brooks[5] in 1886, and has been elaborated upon more recently by others.[6,23] Clinically, myocardial ischemia is usually not apparent until several weeks after birth when the difference between the systemic and pulmonary arterial pressures becomes established.[22] Death occurs between the age of 2½ to 13 months in the majority of cases.

Roentgenoscopy shows markedly diminished pulsations along the left ventricular border. Cardiomegaly, primarily due to left ventricular enlargement, is present on roentgenography. Left atrial enlargement with posterior displacement of the barium filled esophagus occasionally occurs, and is generally due to mitral insufficiency. Atelectasis of 'the left lower lobe is common and is probably due to compression of the left lower lobe bronchus by the heart.[15] Atelectasis of part of the right lung may also occur (Fig. 1*A*). Visualization of the anomalous coronary artery by aortography or selective coronary arteriography provides the definitive diagnosis (Fig. 3, *A* to *F*). Opacification of part of the left coronary artery during intravenous angiocardiography, selective pulmonary, or right ventricular injection may also be secured (Fig. 2, *C* and *D*). Other findings of serial angiocardiography and cineangiocardiography include prolonged opacification of an enlarged, thick-walled left ventricle with poor contraction of the left ventricle and little change in volume following systole. Consequently, poor opacification of the aorta follows. In contrast, the left atrium pulsates vigorously and ejects opacified streams of blood into the sac-like, dilated left ventricle. The right ventricle is surrounded and displaced anteriorly, superiorly, and appears to be displaced to the right by the huge left ventricle (Fig. 2, *A*, *B*, *C* and *D*; and Fig. 4, *A* and *C*).

Endocardial fibroelastosis, glycogen storage disease, and myocarditis should be considered in the differential diagnosis. Glycogen storage disease can usually be recognized clinically, especially if muscle weakness is present; muscle biopsy in such cases is often diagnostic.[9] Myocarditis and endocardial fibroelastosis are more difficult to differentiate from anomalous origin of the left coronary artery.[17] However, the clinical history, age of onset, and electrocardiographic findings are helpful in the differential diagnosis. Angiocardiography and coronary arteriography establish the definitive diagnosis. The prognosis of a patient with anomalous origin of the left coronary artery from the pulmonary artery is poor. Survival to adulthood occurs in only about 15 per cent of the cases. Ligation of the anterior descending branch of the left coronary artery in our case was followed by death.

By virtue of the difference in magnitude and direction of blood flow through the left coronary artery and the capacity of the anastomoses, the manifestations of the anomaly vary from patient to patient and result in a spectrum of clinical and pathologic findings.[8,9] At one extreme are the infants without functionally useful collaterals between the coronary arteries. These generally die within the first year of life. At the other end of the spectrum are those with capacious collaterals; in effect, those who have survived infancy. In an intermediate group are those who have survived the neonatal period but have evidence of myocardial damage. This group of patients is best evaluated by cardiac catheterization and by coronary arteriography.[19]

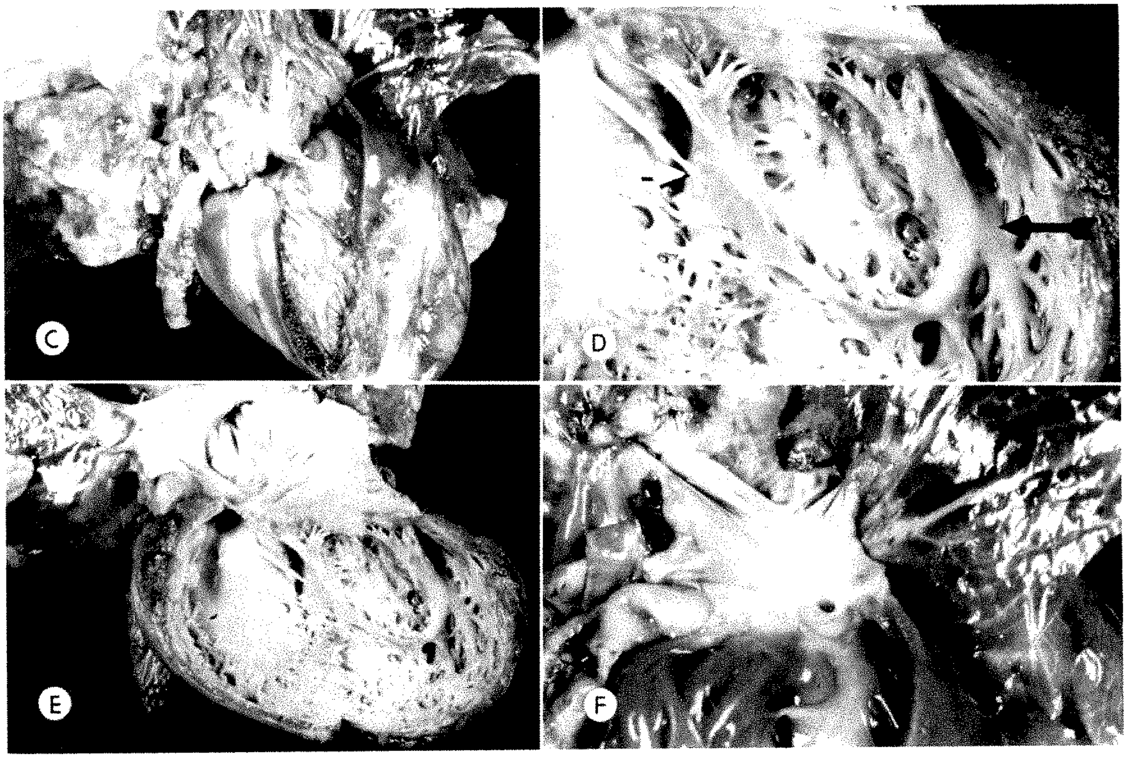


FIG. 4. (*C*) Anterior view of the heart (opened) showing normal-sized right ventricle surrounded on three sides by the left ventricle. (*D*) Mitral valve and papillary muscles showing retraction of the anterior leaflet of the mitral valve, atrophy of the anterior papillary muscle (white arrow), a relatively normal-sized posterior papillary muscle (black arrow), and endocardial sclerosis. (*E*) Left atrium and ventricle showing dilatation of both chambers and marked, opaque, fibroelastic thickened endocardium. (*F*) Right ventricle, pulmonic valve and pulmonary arteries showing ostium of left coronary artery.

cardiography demonstrated coarctation of the aorta with a short small-caliber aortic segment beyond the left subclavian artery, poststenotic dilatation of the descending aorta, and markedly enlarged internal mammary arteries (Fig. 3, *B* and *C*). Resection of the coarcted aorta was performed on March 8, 1961. The patient had an uneventful postoperative course. On discharge, he was well and normotensive in all extremities.

In December, 1963, he was re-examined because of substernal pain following a wrestling match, and hypertension in the upper extremities and absent pulses and blood pressures in the lower extremities were found. Physical examination in the hospital revealed arm blood pressures of 140/70 and leg pressures of 90/70 mm. Hg. The roentgenogram of the chest (Fig. 3*D*) was unchanged. Percutaneous right axillary arteriography revealed bicuspid aortic valves, a 2 by 2 cm. aneurysm at the prestenotic portion of the aorta, and persistent aortic coarctation (Fig. 3, *E*, *F* and *G*).

The patient was re-operated and a localized dissecting aneurysm at the site of a ruptured suture which had caused aortic occlusion was found. The false aneurysm was excised, a prosthesis inserted and the aorta re-anastomosed. Following this, the patient's blood pressure in the upper and lower extremities returned to normal.

DISCUSSION

The association of aneurysmal dilatation of the aortic sinuses and coarctation of the aorta has been previously noted.[2,6,8] Postoperative aortographic studies of such cases have been rare. In Case I, comparison of the preoperative aortogram (Fig. 1*B*) with the study made 10 years later (Fig. 1*C*) shows marked enlargement of the aortic sinuses. In the latest study the aortic regurgitation is striking. Since the lumen of the aorta at the arch was now patent and without a pressure gradient, it is apparent that repair of the coarctation did not halt further enlargement of the aortic sinuses and development of frank aortic regurgitation. Correction of the aortic insufficiency would require an artificial valve replacement—a formidable undertaking at the present time, especially in the presence of the aortic sinus aneurysm.

Re-stenosis of the thoracic aorta probably occurred in the second patient because the operation was performed at the age of 2 years, at a time before the aorta had attained sufficient size to provide an adequate lumen in later life. Because a preoperative aortogram was not obtained in this patient, the extent of enlargement of the aortic sinus aneurysm is unknown. Comparison of the conventional roentgeno-

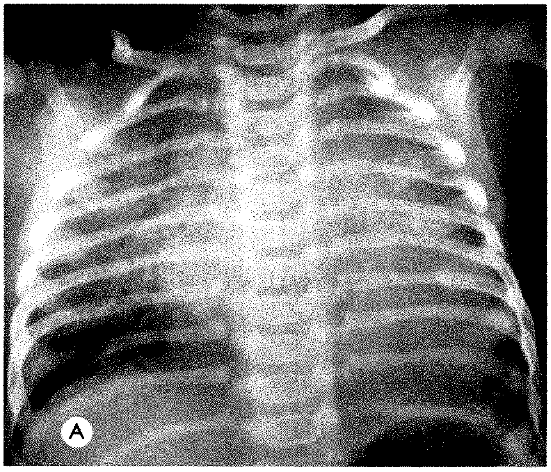


Fig. 2. Case II. (*A*) Frontal roentgenogram showing severe congestive heart failure in a 3 month old infant with coarctation of the aorta.

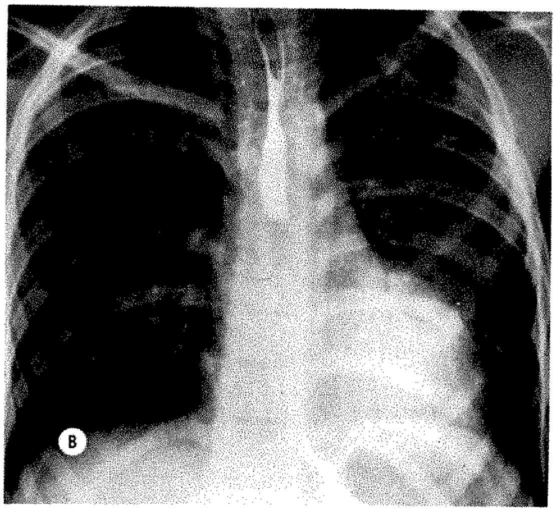


Fig. 2. (*B*) Frontal esophagram made 7 years after surgery for correction of aortic coarctation showing left ventricular enlargement and dilatation of the ascending aorta. The aortic knob is hypoplastic and a "3" sign is present. No rib notching is seen.

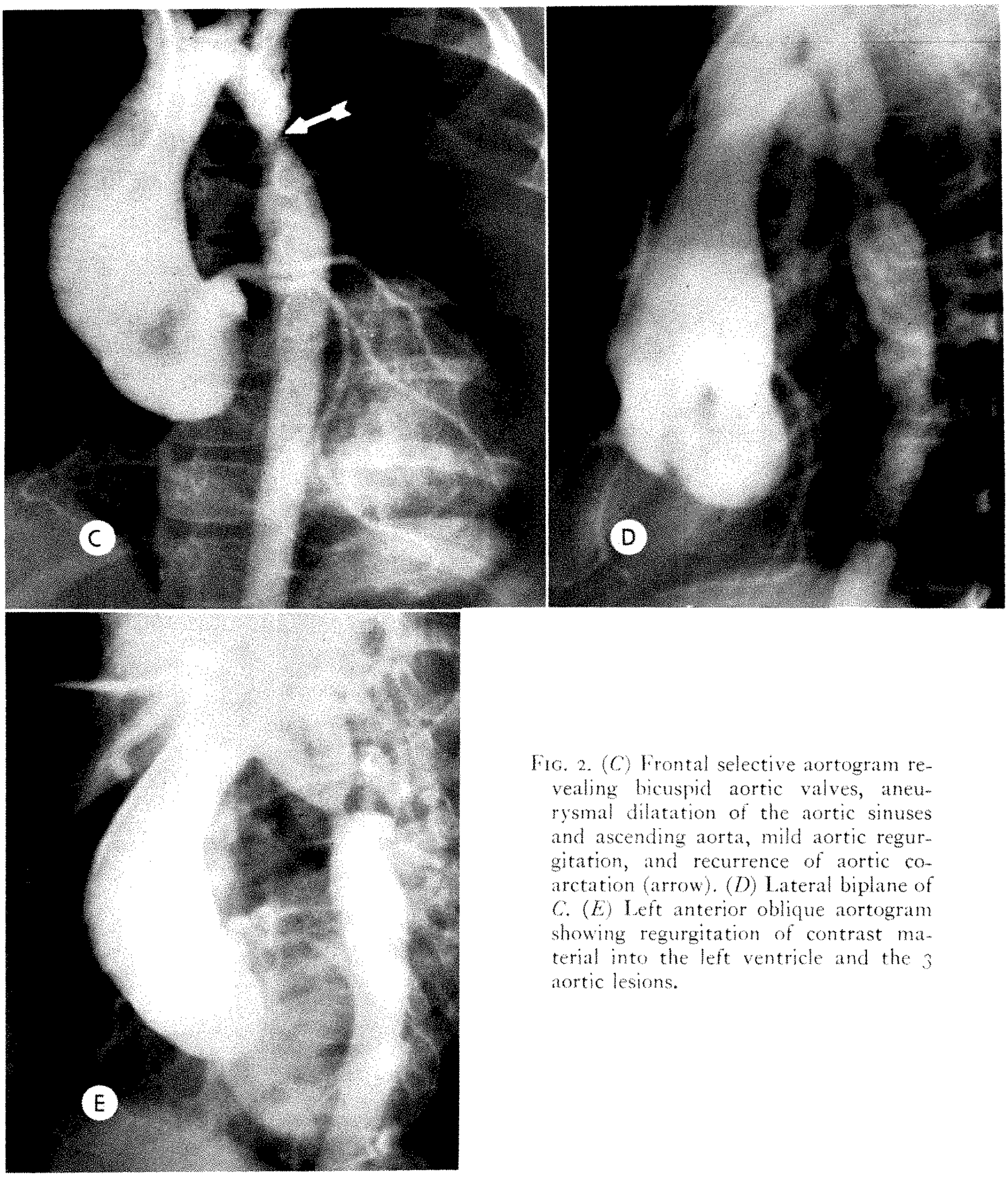
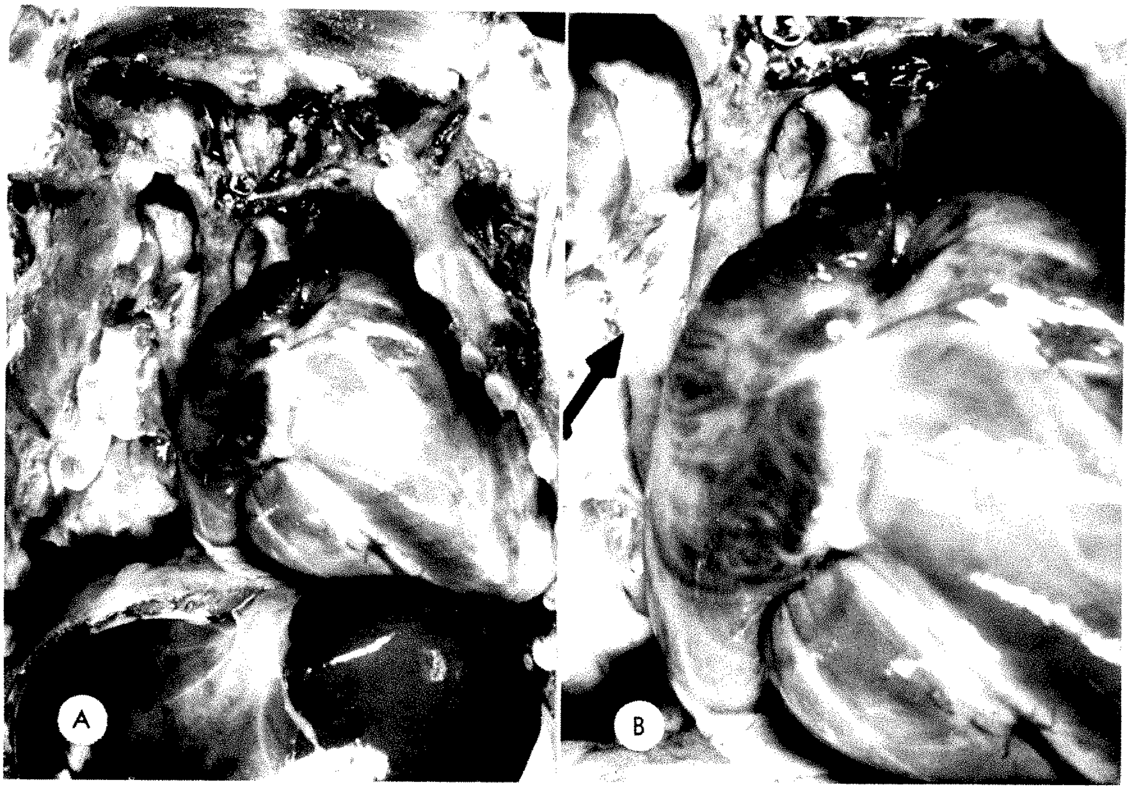


Fig. 2. (*C*) Frontal selective aortogram revealing bicuspid aortic valves, aneurysmal dilatation of the aortic sinuses and ascending aorta, mild aortic regurgitation, and recurrence of aortic coarctation (arrow). (*D*) Lateral biplane of *C*. (*E*) Left anterior oblique aortogram showing regurgitation of contrast material into the left ventricle and the 3 aortic lesions.

gram (Fig. 2*A*) with that made 9 years later (Fig. 2*B*) suggests, however, that aneurysmal dilatation of the aortic sinuses and ascending aorta was present from the beginning. However, since the murmur of aortic insufficiency appeared later, it seems safe to conclude that the aortic valve incompetence is of more recent duration. The mild degree of aortic regurgitation found in the aortograms also bears this out (Fig. 2, *C*, *D* and *E*). In this child, re-operation for correction of the coarctation is based on the usual indications. The mild degree of aortic insufficiency is as yet of no great significance, and operation with cure of the hypertension may prevent further



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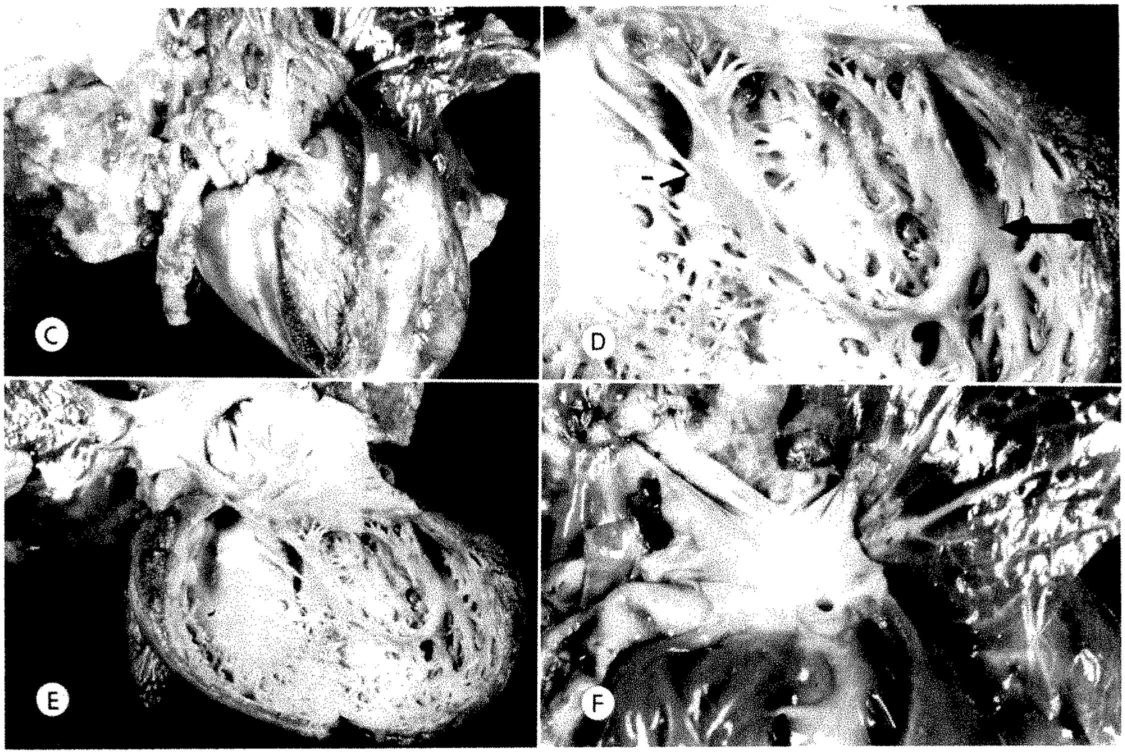

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If extensive collaterals and a left-to-right shunt are demonstrated, ligation of the left coronary artery may be beneficial. It is assumed that this fistulous flow partially bypasses the capillary bed, and that ligation of the anomalous left coronary artery increases capillary perfusion. However, at least one asymptomatic 16 year old girl developed myocardial infarction following operation.[18] Poudrage and banding of the pulmonary artery have been recommended by some,[13,20] and these procedures may be of value in the intermediate group. Anastomosis of the aberrant coronary artery with a systemic artery has also been advocated.[25] This has been attempted but was unsuccessful.[13] In our case, since bidirectional left coronary blood flow was demonstrated even though the left-to-right shunt was predominant, coronary arterial ligation was probably premature.

SUMMARY AND CONCLUSIONS

The techniques of intravenous angiocardiography and selective aortography established the diagnosis of anomalous origin of the left coronary artery from the pulmonary artery in a 4 month old infant. Bidirectional flow in the left coronary artery with predominant left-to-right shunt and extensive collateral circulation was demonstrated. Ligation of one branch of the left coronary artery proved fatal. Necropsy permitted correlation of the roentgenographic and pathologic findings.

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ANEURYSMS COMPLICATING THE POSTOPERATIVE COURSE OF COARCTATION OF THE AORTA*

REPORT OF 3 CASES

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MYCOTIC aneurysms, though uncommon, may occur at the pre- or post-stenotic sites of coarctation of the thoracic aorta.[12] Aneurysmal dilatation of the aortic sinuses associated with coarctation of the aorta has been reported more often and may be present in about 4 per cent of the patients investigated by means of angiocardiography preoperatively.[8] Recently, and within a period of 1 week, 3 patients with aneurysms, 2 of the aortic sinuses and the other at the prestenotic aortic portion of a re-stenotic coarctation of the arch of the aorta, were encountered at this center. These lesions were discovered 10, 9 and 2 years, respectively, following resection of the coarcted segment and re-anastomosis of the aorta. The roentgen features and diagnosis of the aneurysms are herein described, and are the reasons for this report.

REPORT OF CASES

CASE I. *Enlargement of aortic sinus aneurysm and moderate to severe aortic regurgitation despite repair of coarctation of the aorta.* A 20 year old college student[13] was first seen at the age of 10 years because of hypertension in the arms of 150/80 and in the legs of 70/40 mm. Hg. The pulses in the groin and legs were markedly decreased. The conventional roentgenogram showed slight prominence of the left ventricle but no rib notching (Fig. 1*A*). Intravenous angiocardiography made in June, 1954 in the erect left anterior oblique position, disclosed an adult type of coarctation of the aorta and mild dilatation of the aortic sinuses (Fig. 1*B*). Following repair of the coarctation, the pulses in the lower extremities were palpable and the blood pressure became normal in all extremities.

In December 1963, ten years later, he was re-admitted because of severe headaches, dizziness, and episodes of syncope. He had clinical signs of aortic regurgitation but the blood pressure was not elevated, being 130/60-40 mm. Hg in the lower extremities. Percutaneous right axillary selective aortography revealed aneurysmal dilatation of the aortic sinuses, bicuspid aortic valves, moderate to severe aortic regurgitation, and a dilated left ventricle. The aorta, at the site of the previous coarctation, was patent and the intra-aortic blood pressure was 130 mm. Hg (Fig. 1*C*). There was no gradient across the site of the previous coarctation.

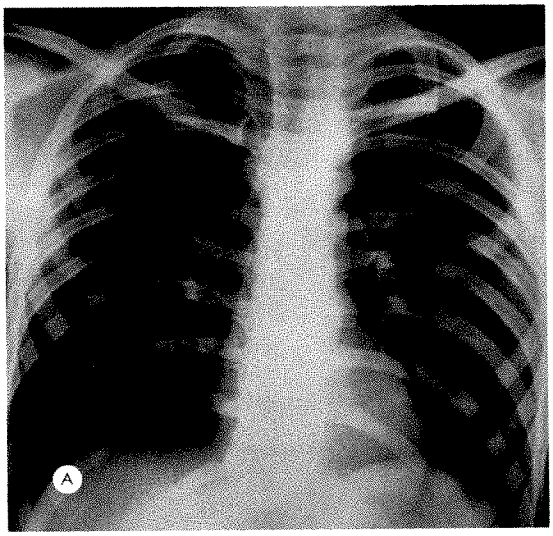

FIG. 1. Case I. (*A*) Teleroentogenogram of the chest showing slight prominence of the left ventricle without rib notching.

CASE II. *Bicuspid aortic valves, mild aortic regurgitation, aortic sinus aneurysm, and recurrent stenosis of aortic coarctation.* A 3 month old infant was first seen in March, 1954 because of congestive heart failure (Fig. 2*A*). Coarctation of the aorta was diagnosed on clinical grounds because of hypertension, 170/110 mm.

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Hg in the arms, with unobtainable blood pressures in the lower extremities. Digitalization alleviated the heart failure but resection of the coarctation was performed 2 years later on April 23, 1956, because of severe hypertension and enlargement of the left atrium and ventricle. Although his general condition had improved and the pulses in the legs and feet became palpable, elevation of the blood pressure in the upper extremity persisted and a diastolic murmur of aortic regurgitation appeared at the age of 8 years. On re-admission on December 15, 1963, enlargement of the left ventricle, mild dilatation of the ascending aorta, and a deformed aortic arch were noted (Fig. 2*B*). A percutaneous right axillary aortogram showed bicuspid aortic valves, aneurysmal dilatation of the aortic sinuses, aneurysmal dilatation of the ascending aorta, and mild aortic regurgitation. The blood pressure in the right arm was 132/90, the left arm was 130/80, and the left leg was 106/90 mm. Hg. In addition, persistence of coarctation of the aorta was evident (Fig. 2, *C*, *D* and *E*). The gradient across the coarctation was 25 mm. Hg.

The patient was re-operated on March 16, 1964. The coarctation was excised and an end-to-end anastomosis of the aorta made. Blood pressures one month later were as follows: right arm, 118/70 mm.; left arm, 110/70 mm.; and left leg, 114/80 mm. Hg.

CASE III. *Prestenotic aortic aneurysm and restenosis of coarctation of the aorta.* A 14 year old boy was first seen in March, 1961, when he was 12 years old, because of hypertension of the upper extremities (right arm, 150/80 and left arm, 140/70 mm. Hg) and absent pulses and blood pressure in the lower extremities. The conventional roentgenogram of the chest (Fig. 3*A*) showed slight dilatation of the ascending aorta. Biplane simultaneous intravenous angio-

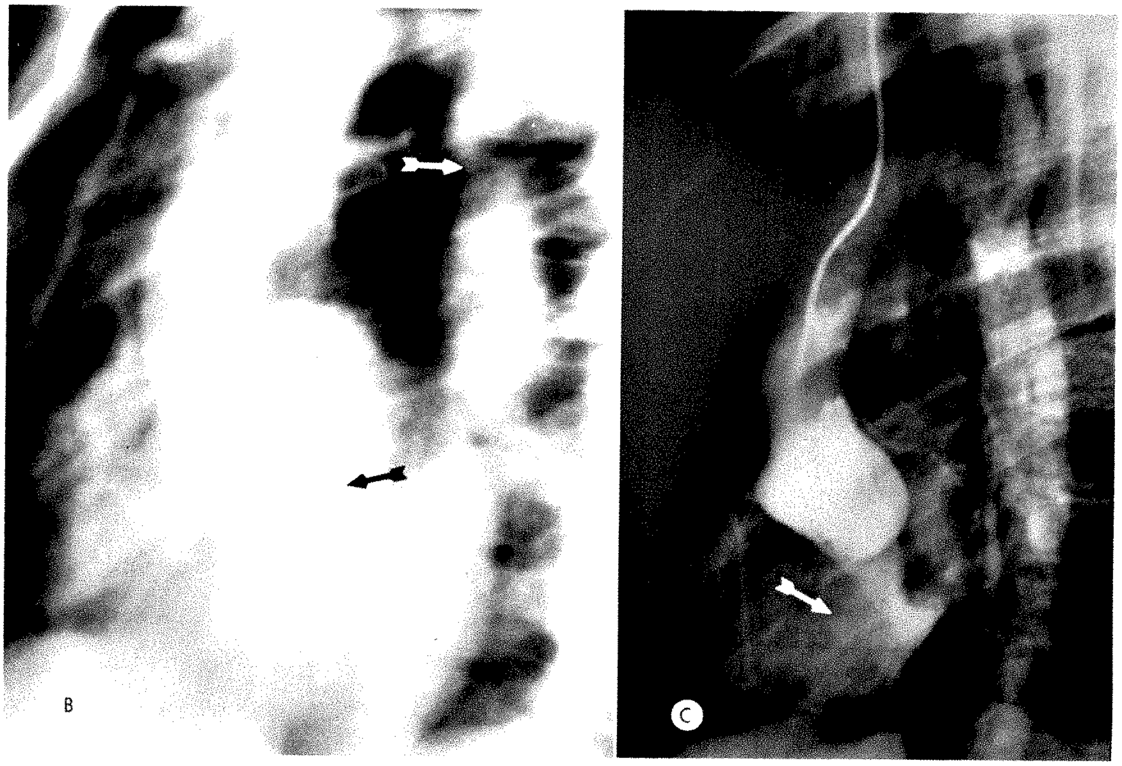

FIG. 1. (*B*) Preoperative intravenous angiocardiogram, made in 1954, showing an aortic sinus aneurysm (lower arrow) and coarctation of the aorta (upper arrow). (*C*) Percutaneous right transaxillary aortogram in left anterior oblique projection made 10 years later showing bicuspid aortic valves, an aortic sinus aneurysm, and moderate aortic regurgitation (arrow). Note that the aortic arch lumen is intact and that blood flow in the descending aorta is good. Separate orifice for the anterior descending and circumflex branches of the left coronary artery is also present. (Republished by permission of the American Heart Association, Inc.[13])

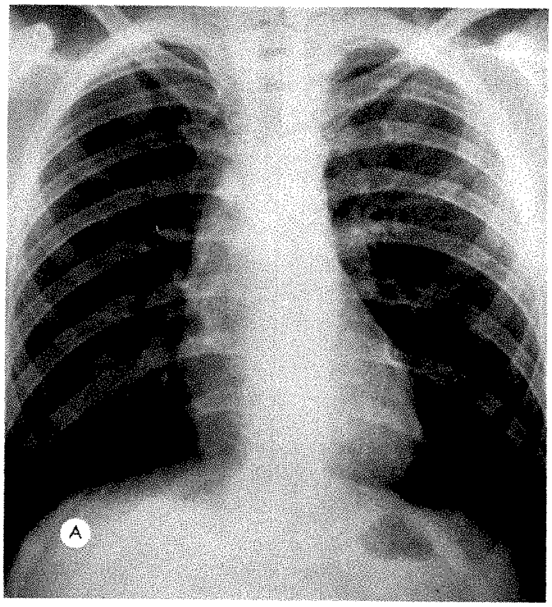

Fig. 3. Case iii. (*A*) Frontal teleroentgenogram of the chest made in 1961 showing slight prominence of the left ventricle and ascending aorta. Rib notching is not present

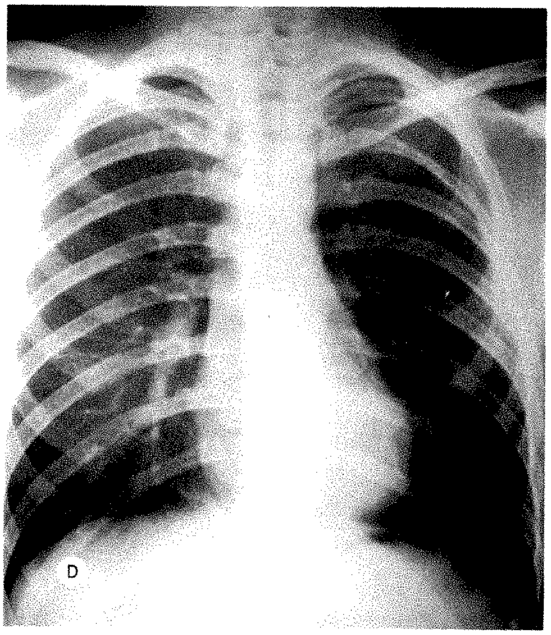

Fig. 3. (*D*) Frontal teleroentgenogram of the chest, 2 years later, showing prominence of the left ventricle but the ascending aortic silhouette appears normal.

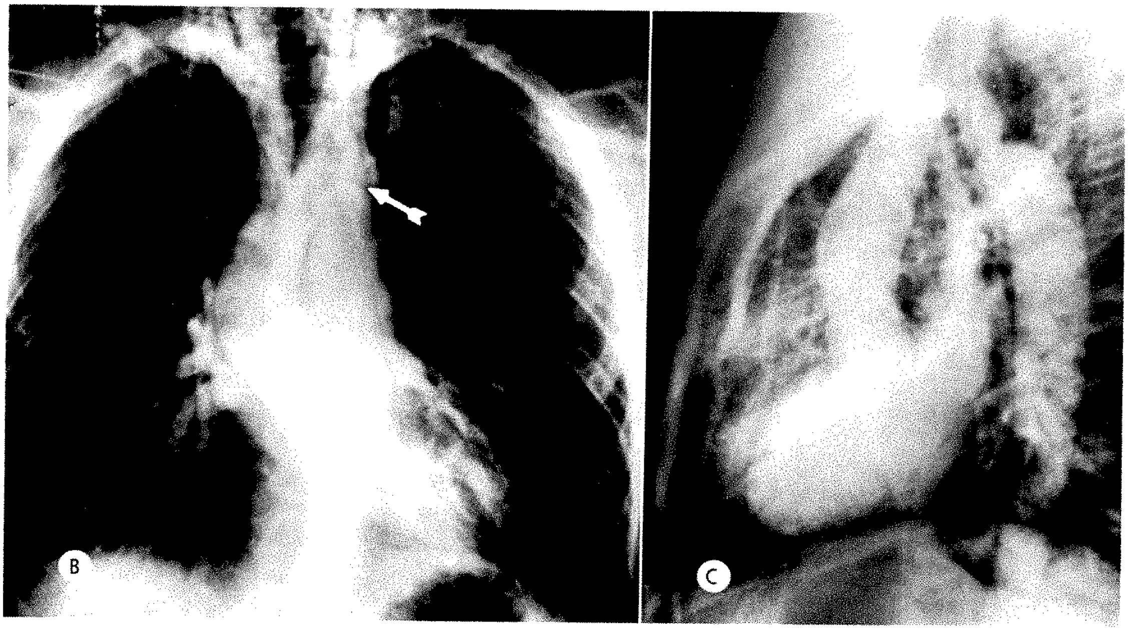

Fig. 3. (*B*) Frontal intravenous angiocardiogram showing the site of coarctation of the aorta (arrow) and large internal mammary and shoulder arterial collaterals. (*C*) Simultaneous, lateral biplane aortogram of *B*.

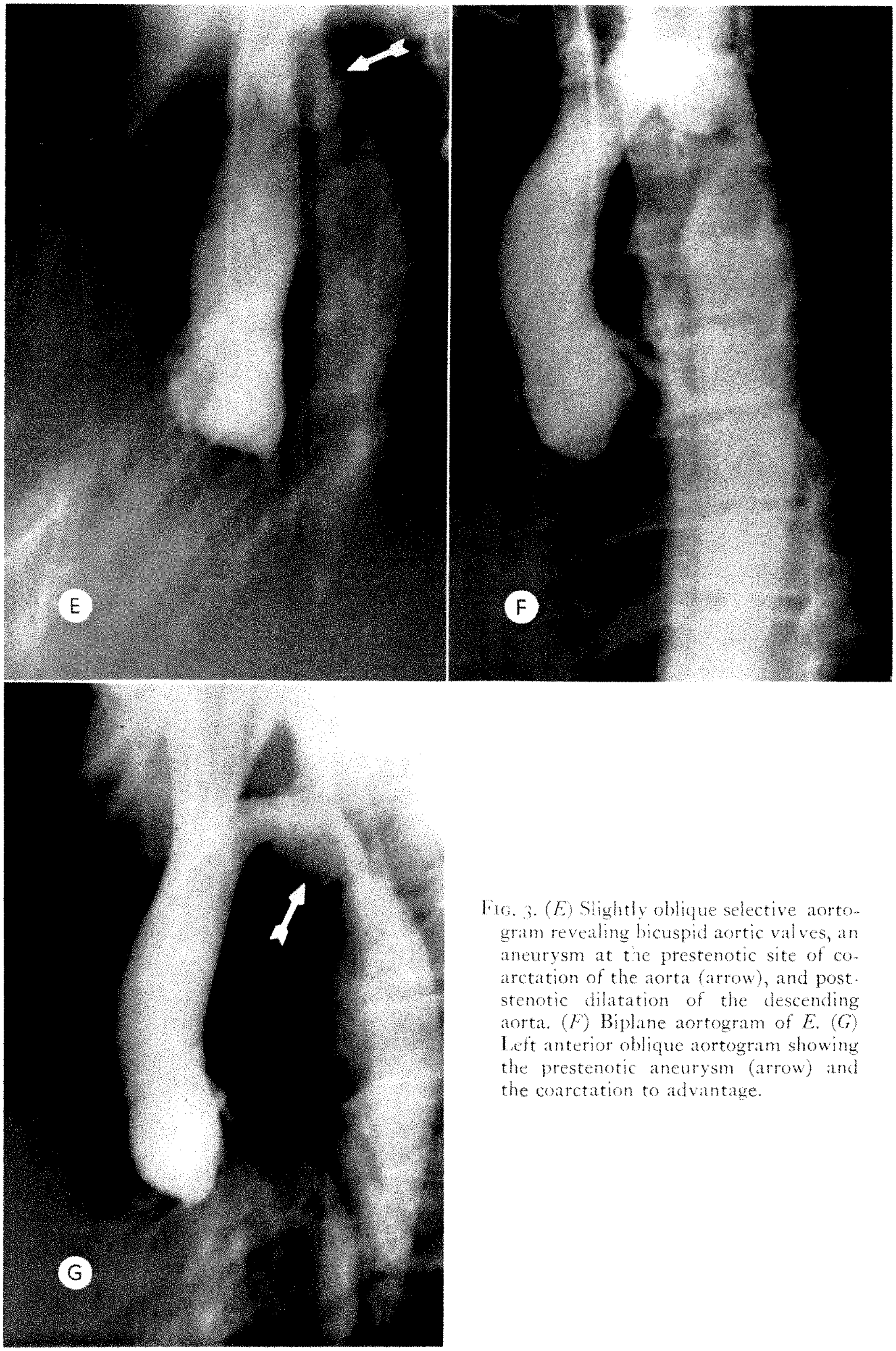

Fig. 3. (*E*) Slightly oblique selective aortogram revealing bicuspid aortic valves, an aneurysm at the prestenotic site of coarctation of the aorta (arrow), and poststenotic dilatation of the descending aorta. (*F*) Biplane aortogram of *E*. (*G*) Left anterior oblique aortogram showing the prestenotic aneurysm (arrow) and the coarctation to advantage.

dilatation of the aortic sinuses, although the data in this case suggest that this may not be related.

The last case is unique in that development of a prestenotic aortic aneurysm and obstruction of the aorta at the site of resection have not, to our knowledge, been previously reported. Absence of a febrile course and negative blood cultures ruled out a prestenotic mycotic aneurysm.[12] The pathogenesis of the lesion and the cause of the occlusion of the descending aorta were due to a small dissecting aneurysm which resulted from a ruptured suture. Unlike the case recently reported,[11] a hematoma following operative repair of coarctation seems unlikely because of the saccular appearance of the aneurysm without surrounding thrombus. That intravenous angiocardiography can establish the diagnosis of coarctation of the aorta by showing the point of coarctation and the collateral circulation is demonstrated in Figures 1*B* and 3, *B* and *C*. The detailed anatomy of the aortic cusps is obscured in the angiocardiogram because of opacification of the neighboring cardiac chambers. It is also difficult, if not impossible with the method of intravenous aortography, to determine whether the aortic valves are bicuspid. Similarly, with this technique the origins and ramifications of the coronary arterial system are obscured; however, the aortic sinuses can be visualized (Fig. 1*B;* and 3, *B* and *C*).[5–10] The degree of aortic insufficiency and whether there is rupture of an aortic sinus aneurysm cannot be demonstrated with the intravenous method. Therefore, selective aortography with the catheter at the aortic root is necessary for, and is the method of choice of, visualization of the aortic valve cusps, aortic sinuses, coronary arterial system, and aortic insufficiency (Fig. 1*C;* 2, *C*, *D* and *E;* and 3, *E*, *F* and *G*).

Although in Case I repair of the coarctation was successful, it did not prevent the enlargement of the aortic sinus aneurysm and the development of aortic valve incompetence with moderate to severe aortic regurgitation. It would appear, therefore, that the demonstration of an aortic sinus aneurysm associated with coarctation of the aorta may be of ominous significance. However, this does not mean that correction of the coarctation should not be undertaken. Indeed, there is the hope, although not realized in Case I, that creation of normotensive pressures may arrest the growth of the aneurysm or prevent the development of aortic valve incompetence.

The etiology of the aortic sinus aneurysm and the ascending aortic dilatations in Case II (Fig. 2, *C*, *D* and *E*) is unknown. To our knowledge, pathologic study of such lesions in association with coarctation of the aorta has not been carried out. That there may be medial degeneration of the aorta in the aortic sinus aneurysm and also of the ascending aorta in Case II seems probable. In Marfan's syndrome aortic sinus aneurysm with medial degeneration of the aortic sinuses is common.[5,6,9] Furthermore, Wagenvoort and associates[14] in a recent communication stated that they were unable to tell the difference histologically between the medial degeneration of the aorta occurring in Marfan's syndrome and that of idiopathic medial degeneration of the aorta. Accordingly, medial degeneration of the aortic sinus and ascending aorta may also be the lesion in patients with coarctation.

All 3 patients in this series had bicuspid aortic valves. A high incidence of bicuspid aortic valves in coarctation of the aorta (25 per cent) was noted by Hamilton and Abbott.[4] This anomaly has been recognized to be a forerunner of aortic stenosis and insufficiency.[1,3] Only the 2 patients with aortic sinus aneurysms had aortic insufficiency. It may be, therefore, that uncomplicated bicuspid aortic valves do not become stenotic or insufficient until late in life at a time when degenerative arteriosclerotic lesions begin to appear. An isolated aortic sinus aneurysm (Fig. 1*A*) in contrast to that with associated ascending aortic dilatations (Fig. 2, *A* and *B*) does not show dilatation of the ascending aortic portion of the cardiac silhouette. It is, therefore, important to perform aortic contrast studies whenever aortic sinus aneurysms are suspected even though the cardiac silhouette is normal.[5,9] Routine preoperative aortography to substantiate the diagnosis of coarctation of the aorta has long been advocated; it is also important for visualization of the root of the aorta in order to diagnose bicuspid aortic valves, aortic sinus aneurysms, and aortic insufficiency.

SUMMARY AND CONCLUSIONS

Aneurysms complicating surgical correction of coarctation of the aorta are rare. A sinus of Valsalva aneurysm was demonstrated preoperatively by intravenous angiocardiography in the first case. In a 10 year period, despite creation of an adequate aortic lumen following surgical resection of the coarctation, the aneurysm increased in size and incompetent bicuspid valves caused moderate to severe aortic regurgitation. In the second case, aortic stenosis reoccurred at the site of operation, resulting in a 25 mm. Hg gradient of pressure across the descending aorta. A large aortic sinus aneurysm, aneurysmal dilatation of the ascending aorta, and bicuspid aortic valves were revealed by aortography 9 years later. In this instance the aortic regurgitation was only minimal. In the last case, a saccular aneurysm was visualized proximal to the recurrent coarctation of the aorta. The aneurysm was due to localized dissection of the sutured aorta.

Preoperative selective aortography is recommended, especially when murmurs are elicited at the root of the aorta, in all cases of coarctation of the aorta. Angiography, of course, is indicated whenever there are postoperative complications such as the development of new aortic murmurs, failure to reduce hypertension, or recurrence of signs of coarctation.

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CONGENITAL VARIATIONS IN CEPHALOBRACHIAL VESSELS IN ANENCEPHALY*

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ANENCEPHALY, the most frequent anomaly incompatible with life, is the most common congenital malformation of the cranium. It occurs about 1.6 to 5.9 times per 1,000 births in the general population. Little is known of its etiology. According to Laurence,[6] studies[5,7,10,11] of human embryos indicate that the causative factor acts between the 16th and 26th day after conception. A genetic factor is suggested by the familial incidence of the condition. Twin studies, however, have not proved convincing and, as yet, chromosomal studies have not been particularly revealing. Associated anomalies of the vertebral column and the spinal cord often coexist. Malformations of the gonads, the pituitary, adrenal and thyroid glands, hypoplasia of the lungs, gastrointestinal malformations and diaphragmatic hernias and malformations of the extremities also occur.[7]

No mention is made of the existence of cardiovascular anomalies with anencephaly. Therefore, the identification of a definite malformation of the cephalobrachial vessels in one anencephalic infant and of an infrequently observed structural variation in these vessels in a pair of monozygotic anencephalic twins is of interest. These were observed in 3 out of 5 consecutive anencephalic infants; the aortic arch and the cephalobrachial vessels were normal in the other two. No cardiac malformations were present in any of the 5 infants. The vascular changes were noted on postmortem roentgenograms made after the injection of a barium-water suspension into the left ventricle or the ascending aorta, and were confirmed by inspection of the organs at necropsy.

REPORT OF CASES

CASE I. A 38 year old white woman was delivered of an 1,800 gm. male anencephalic infant during the 36th week of gestation. There was no antenatal history of trauma, infection, or exposure to noxious agents. Five siblings were normal. The heart and great vessels were normal (Fig. 1); the adrenals, thyroid, and the left kidney were hypoplastic.

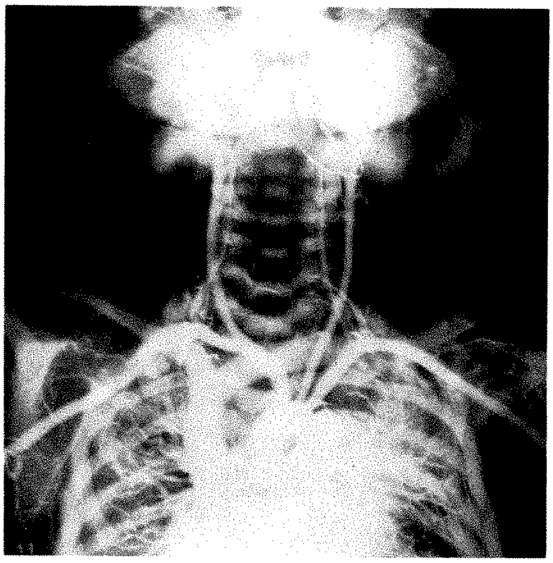

FIG. 1. Case I. Postmortem roentgenogram of cephalobrachial vessels after the injection of the aorta and right atrium with barium suspension. The innominate artery originates from the aortic arch in its normal position, as does the left common carotid and left subclavian artery.

CASE II. A 22 year old white woman was delivered of a stillborn anencephalic male infant weighing 1,550 gm. during the 36th week of gestation. The antenatal history was unremarkable. The heart and aorta were normal; the adrenals were hypoplastic.

CASE III. A 25 year old white woman was delivered at term of a stillborn anencephalic female infant weighing 3,300 gm. The antenatal history was unremarkable. One living sibling was normal. The aortic arch was in its usual position. The right common carotid artery

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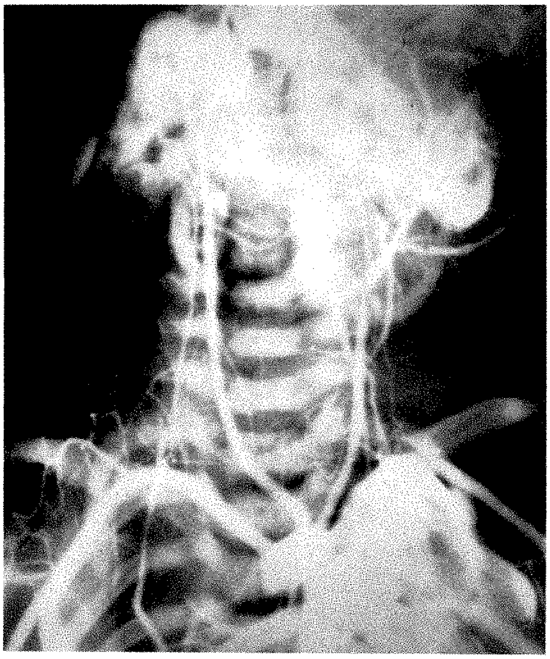

Fig. 2. Case iii. Postmortem injection of the aorta. The right subclavian artery originates directly from the aortic arch. Distal to this is the right common carotid artery and immediately adjacent thereto is the left common carotid artery. The left subclavian artery arises distal to the left common carotid artery.

originated directly from the right side of the transverse thoracic aorta. Immediately distal to this was the origin of the left common carotid arteries. Both subclavian arteries arose directly from the aortic arch, the right proximal to the right carotid artery and the left distal to the left common carotid artery. The vertebral arteries emerged from the subclavian arteries in their usual situations (Fig. 2). Both adrenals were hypoplastic.

Cases iv and v. A 26 year old white woman was delivered of monozygotic twin anencephalic male infants, each weighing 1,750 gm. The anomalous infants had been clearly identified on prepartum abdominal roentgenograms. Twin A (Case iv) survived for 3 days and twin B (Case v) for 10 minutes. The antenatal history was unremarkable except for hydramnios. The placenta was monochorionic-diamniotic, with associated polyhydramnios in Twin B. Both infants had normal hearts. The innominate artery in each was normal. The right subclavian artery extended directly from the innominate artery, and the right common carotid artery proceeded cranially in the usual fashion. The right vertebral artery originated from the right brachial artery normally. The left common carotid artery arose from the medial aspect of the innominate artery about 1 cm. above its junction with the aorta. The left subclavian artery stemmed from the aortic arch distal to the innominate artery. The left vertebral artery was normal (Fig. 3).

COMMENT

Anencephaly usually is attributed to maldevelopment of the brain associated with failure of fusion of the neural tube at about the 4th week of gestation.[13] The term "anencephaly" is not particularly accurate because the condition basically is one of absence of the cranial vault. The base of the skull and the facial bones exist as heavy, thick structures and present an

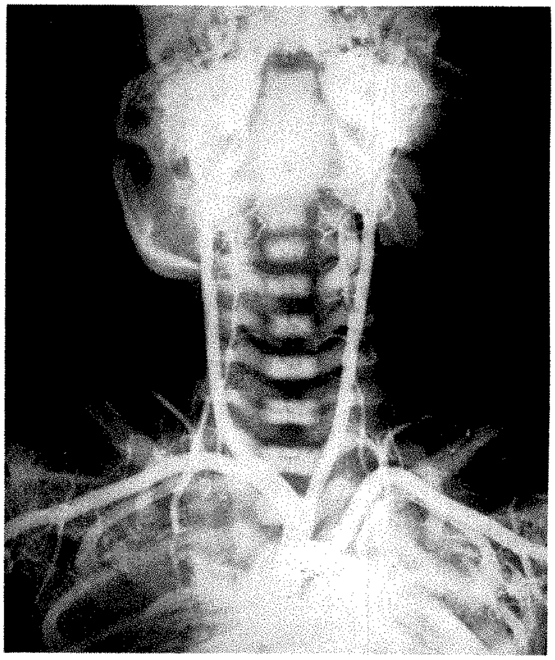

Fig. 3. Case v. Postmortem injection of the aorta. The innominate artery arises in a rather high position from the aortic arch. This vessel continues to the right as the right common carotid and subclavian arteries. The left common carotid artery originates from the innominate artery at a point about 1 cm. from its origin. The left subclavian artery takes off about 0.5 cm. distal from the innominate trunk. Both vertebral arteries originate from the subclavian in their usual positions.

abnormal pattern of fusion. The eyes are constantly present. The hypophyseal fossa is small. The existence of brain anlage is manifested by the presence of the eyes, the anterior lobe of the pituitary, and the trigeminal, vagus and hypoglossal nerves.

As a consequence of what is still an unknown cause, the brain is represented by a flat mass of spongy, highly vascularized glial tissue often containing a large quantity of choroidal structures. Indeed, the polyhydramnios seen with anencephaly has been ascribed to this secretory component.[2] No formed parts of the brain are present above the medulla oblongata. Occasionally, a bit of midbrain or pons is seen, and rarely the cerebellum is formed. A wide range of deformities of the vertebral column and the spinal cord sometimes is concomitant with the maldevelopment of the brain.[13] In the reported 5 anencephalic infants, the vertebrae were normal except for failure of fusion of the neural arches of the upper 3 cervical vertebrae in 3 infants.

Closure of the neural tube occurs at about the fourth week of fetal life. At about the same time the first three aortic arches are present and the fourth is appearing. The subclavian and the vertebral arteries are derived from the fourth arch on the right side. On the left side, the embryonic arch persists as the adult aortic arch. The common carotid arteries are derived from remnants of the third aortic arch. By the sixth week, the first and second arches have degenerated, leaving the third, fourth and sixth. The fifth is never well formed. This time relationship between the closure of the neural tube and the development of the cephalobrachial vessels suggests that the changes seen in Case III, IV and V may have some common cause, even though the neural tube defect is of ectodermal origin and the vascular defect is of mesodermal origin.

The configuration of the cephalobrachial vessels noted in the twin anencephalic infants occurs in but 8 per cent of normal adult aortic arches,[4] and can be regarded as usual.

The pattern present in Case III of both common carotid arteries originating at the upper middle aspect of the aortic arch, quite apart from the subclavian arteries, and the absence of an innominate artery is definitely anomalous.

SUMMARY

In 3 of 5 consecutive anencephalic infants examined by postmortem aortography and subsequently at necropsy, minor changes in the pattern of emergence of the cephalobrachial vessels from the aortic arch were found. One was definitely anomalous and 2 were infrequent but apparently normal variants. In none was there any visible evidence of impedance of normal blood flow from the heart.

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CRANIOLACUNIA

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CRANIOLACUNIA is a term applied by Vogt and Wyatt to a condition previously described in the literature as "Lückenschädel"[3] and "lacunar skull."[1,4] It is characterized by rounded areas of translucency demarcated by dense strips of bone forming a network or weblike pattern (Fig. 1).

Postmortem study reveals defects of the inner table and diploe bordered by thicker bony ridges which represent the width of the intact normal bone, seeming thickened only by comparison with the thin areas. The outer table may also be absent, in which case the dura is in contact with the periosteum. Van Waalwijk van Doorn and Boet[8] have used the term "crainofenestria" to describe this complete bony defect. The gyri of the brain do not conform to the areas of thinning and the brain protrudes into and through the defects in a random fashion without regard for the gyri. The brain frequently exhibits microgyri and hypoplasia of the frontal and occipital lobes.

The etiology of craniolacunia is unknown. Causal theories most often cited are increased intracranial pressure,[4] ischemia secondary to increased pressure,[7] developmental disturbance in ossification,[6] and deficient maternal nutrition.[8]

The purpose of the authors is to report the results of a roentgenologic study of 179 patients who had either spina bifida with meningomyelocele or cranial defect with meningoencephalocele. An additional 2,000 skull examinations of children without meningomyelocele or encephalocele were made for the presence of craniolacunia. Analysis was made with particular emphasis on the roentgen diagnosis, incidence, course and significance and prognosis of craniolacunia.

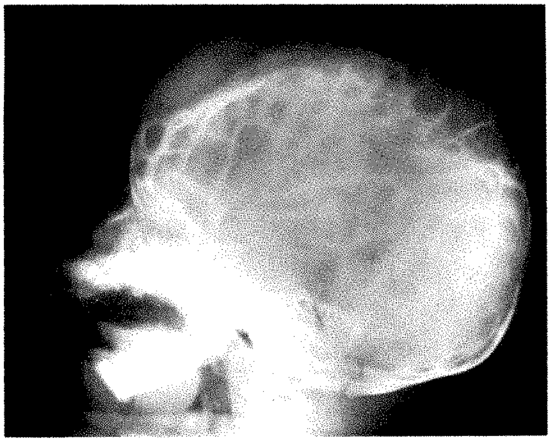

FIG. 1. Typical pattern of craniolacunia. The changes are characteristically localized to parietal, frontal and occipital bones in this order of frequency and severity. Hypo-ossification along margins of frontal bones causes cranium bifidum.

ROENTGEN APPEARANCE

Craniolacunia produces a characteristic pattern of radiolucent areas sharply delineated by distinct strips of dense bone (Fig. 1). Absence of the inner table and diploe causes the roentgen appearance. Tangential roentgenograms reveal only a thin layer of bone, corresponding to the external table, covering the defects. This outer layer is also absent in case of complete defects (craniofenestria) and the bulging soft tissue density of the dura and brain is obvious. The bone adjacent to the sagittal, coronal and lambdoid sutures is selectively involved, the parietal, frontal and occipital bones being most often and most severely affected in this order of frequency.

Decreased ossification of the skull bones is a consistently associated finding and is

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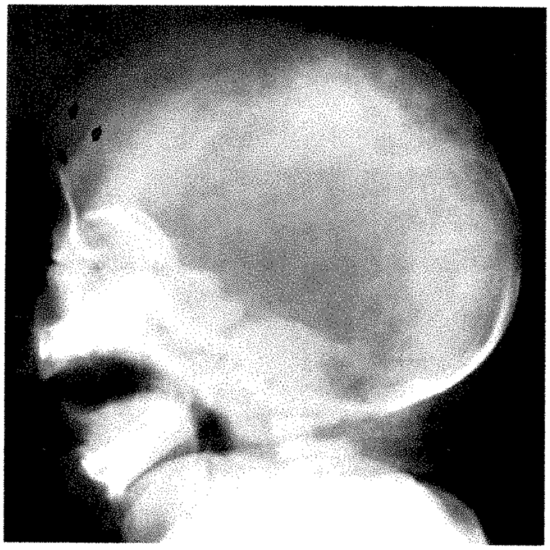

FIG. 2. Craniolacunia is mild in the parietal bones. A large cranium bifidum is present. Ossification of the external table is beginning in the inferior portion of the frontal bones (Arrow 1). The edge of the incomplete frontal bone is indicated by Arrow 2.

manifested by wide sutures which should not be misinterpreted as a sign of increased pressure. The lack of development of the frontal bones frequently results in a cranium bifidum, the gap between the 2 frontal bones in the mid-line measuring 3 to 4 cm. in width, and permitting dura to bulge without producing a true meningoencephalocele (Fig. 1 and 2). Cranium bifidum is occasionally the predominant feature, craniolacunia being mild. The association of cranium bifidum with craniolacunia is so constant that its presence is helpful in the identification of the minor changes of craniolacunia.

Conditions which may be confused with craniolacunia are normal skull markings, craniostenosis, and increased intracranial pressure.

Areas of radiolucency are common in the normal skull (Fig. 3). The density of the skull bones at birth is normally smooth and uniform. The radiolucent markings appear between the ages of 1 and 3 years. They are present to some degree in 75 per cent of all normal skulls between the ages of 1 and 3 years and in 90 per cent between the ages of 3 and 14 years. The thin areas appear to be the result of normal bone growth and development, and the inner table and diploe are always intact. The digital or convolutional markings form a pattern that is quite different from that of marked and moderate craniolacunia, but is similar to that of mild craniolacunia. The location, age incidence, and the absence of craniofenestria and cranium bifidum aid in the differential diagnosis. Sometimes the pattern of these markings is so prominent that increased intracranial pressure is suggested, but it can always be assumed to be normal in the absence of other signs of increased pressure.

Translucent areas with margins of linear density are commonly associated with craniostenosis (Fig. 4). The involved region is always in the bone adjacent to the prematurely closed suture. Characteristic deformity of the skull is caused by failure of bone growth at the stenotic suture. The radiolucent areas are not present at birth and make their appearance about the same time as the normal skull markings. Abnormal bone growth due to the craniostenosis is the most likely explanation for these markings. They do not disappear unless

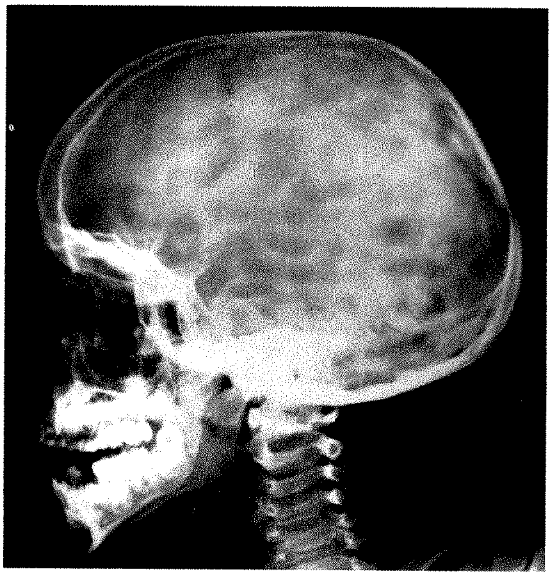

FIG. 3. "Digital" or "convolutional" markings in a normal skull.

there is surgical treatment of the craniostenosis, in which case they diminish in prominence.

Increased intracranial pressure is often listed as a cause for prominence of the skull markings. The fact is that increased pressure does not increase the skull markings prior to normal closure of the sutures between the ages of 8 to 12 years. Lesions causing hydrocephalus in the growing skull separate the sutures without increasing the skull markings. After the sutures have closed, either normally or with craniostenosis, extremely prominent skull markings are caused by increased intracranial pressure (Fig. 5). It is not certain whether these are the result of increased pressure or of abnormal bone growth secondary to the craniostenosis. This appearance is easily differentiated from craniolacunia because it is not present at birth, the involvement is generalized, and there is evidence of craniostenosis. The radiolucent zones are due to thinning, but the inner table and diploe are intact and there is no craniofenestria or cranium bifidum.

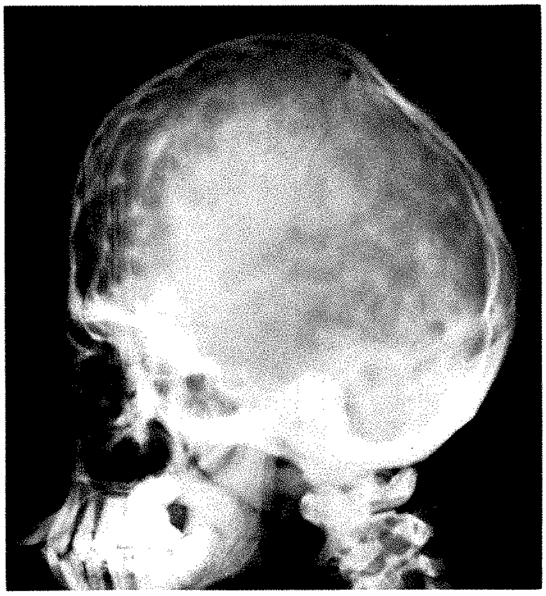

Fig. 4. Brachycephaly due to premature closure of the coronal suture. The zones of radiolucency along the involved suture have an intact inner table and diploe and there is no associated craniofenestria or cranium bifidum.

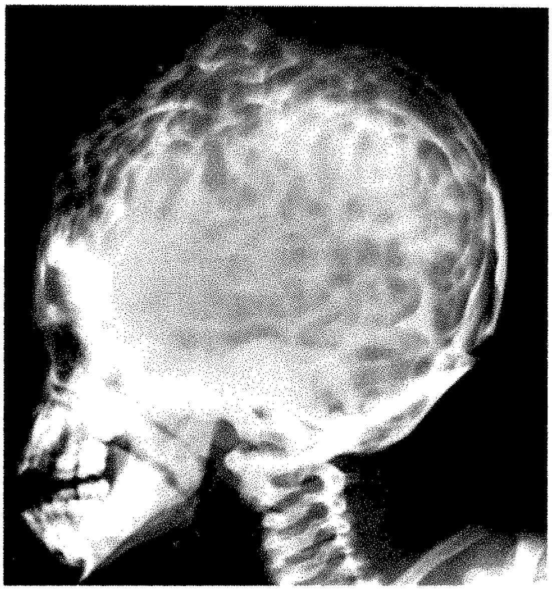

Fig. 5. Generalized pattern of radiolucency in association with premature closure of the skull sutures.

INCIDENCE OF CRANIOLACUNIA

Craniolacunia was found in 89 (50 per cent) of the 179 patients with meningomyelocele and encephalocele. The skull examination of the patients with craniolacunia was obtained during the first 3 months of life. Ninety per cent of these were made before the age of 2 months. There was no skull examination in the 90 patients without craniolacunia until after the age of 3 months.

All patients with spinal meningomyelocele had craniolacunia if the skull examination was done prior to the age of 3 months. This incidence of 100 per cent does not necessarily indicate that all patients with meningomyelocele have craniolacunia, but it supports the opinion[2] that it is more common than generally recorded. Vogt and Wyatt report an incidence of 43 per cent in 120 patients with meningomyelocele, but they did not break the skull examinations down into age groups. Thirteen of the 179 patients had encephalocele. Six of these had craniolacunia. One showed radiolucent areas in the posterior parietal bones that were so minimal they were classified as normal, and no mention was made of them in the postmortem study. The other 6 patients did not have a skull examination until after the age of 3 months and none of these revealed craniolacunia. It is interesting that 4 of the 6 cases with craniolacunia had a spinal meningomyelocele in addition to the encephalocele.

The severity of the craniolacunia was graded as marked, moderate and mild. All of those graded as marked were in the skulls of infants less than 1 month of age. Moderate and mild degrees of craniolacunia were seen anytime during the first 3 months of life, but 75 per cent of those judged moderate were in patients below the age of 1 month. There were several instances in which the craniolacunia had completely disappeared before the age of 2 months. These facts indicate that the true incidence of craniolacunia will not be determined unless the skull is roentgenographed within the first month of life, preferably within the first week.

None of the 2,000 skull examinations of patients without meningocele or encephalocele showed craniolacunia. Some skulls exhibited an appearance which could be confused with craniolacunia, but did not meet the criteria required for the diagnosis of this condition. Approximately 300 of these patients were below the age of 6 months at the time of the skull examination, thereby providing a control study of the age group where it is believed craniolacunia will be evident.

COURSE OF CRANIOLACUNIA

The natural course of craniolacunia was observed in 31 patients who had follow-up skull examinations 1 to 10 months after the initial one. The arborizing pattern of craniolacunia quickly disappears in all patients. The thin areas of bone are obliterated by normally appearing ossification. The newly formed bone blends imperceptibly with the dense ridges, resulting in a smooth pattern and leaving no trace of the previous irregularity (Fig. 6, *A*, *B* and *C*). Craniofenestria disappears as rapidly and completely as craniolacunia.

Cranium bifidum also disappears but more slowly than craniolacunia and craniofenestria. The follow-up skull examinations were made at irregular intervals rendering exact determination of the rate of disappearance difficult. It was possible to determine roughly that craniolacunia and craniofenestria disappear by the age of 3 months. The defect of cranium bifidum is several times as large as that of craniolacunia and craniofenestria. It seems logical that ossification of the skull bones proceeds at a constant rate for any given patient and that the differential in the rate of disappearance is related to the size of the defect to be covered.

The presence of hydrocephalus did not affect the rate of disappearance of any of the types of defects.

The craniolacunia and craniofenestria associated with encephalocele cleared as rapidly as with spinal meningomyeloceles. The specific defect through which the encephalocele passed did not clear, however. The patency of the encephalocele defect was documented in 4 patients at ages of 18 months, 2½ years, 8 years, and 12 years.

SIGNIFICANCE AND PROGNOSIS OF CRANIOLACUNIA

The chief significance of craniolacunia is that it is specifically associated with meningocele, meningomyelocele, and encephalocele. This is indicated by the facts that all patients under the age of 3 months with these anomalies had craniolacunia, every patient with craniolacunia had a meningocele or encephalocele, and craniolacunia was not seen in 2,000 skull examinations of patients without meningocele or encephalocele.

Vogt and Wyatt reported that patients with craniolacunia did more poorly than those without it. No attempt was made to assess the prognostic significance of craniolacunia in our group of patients because all

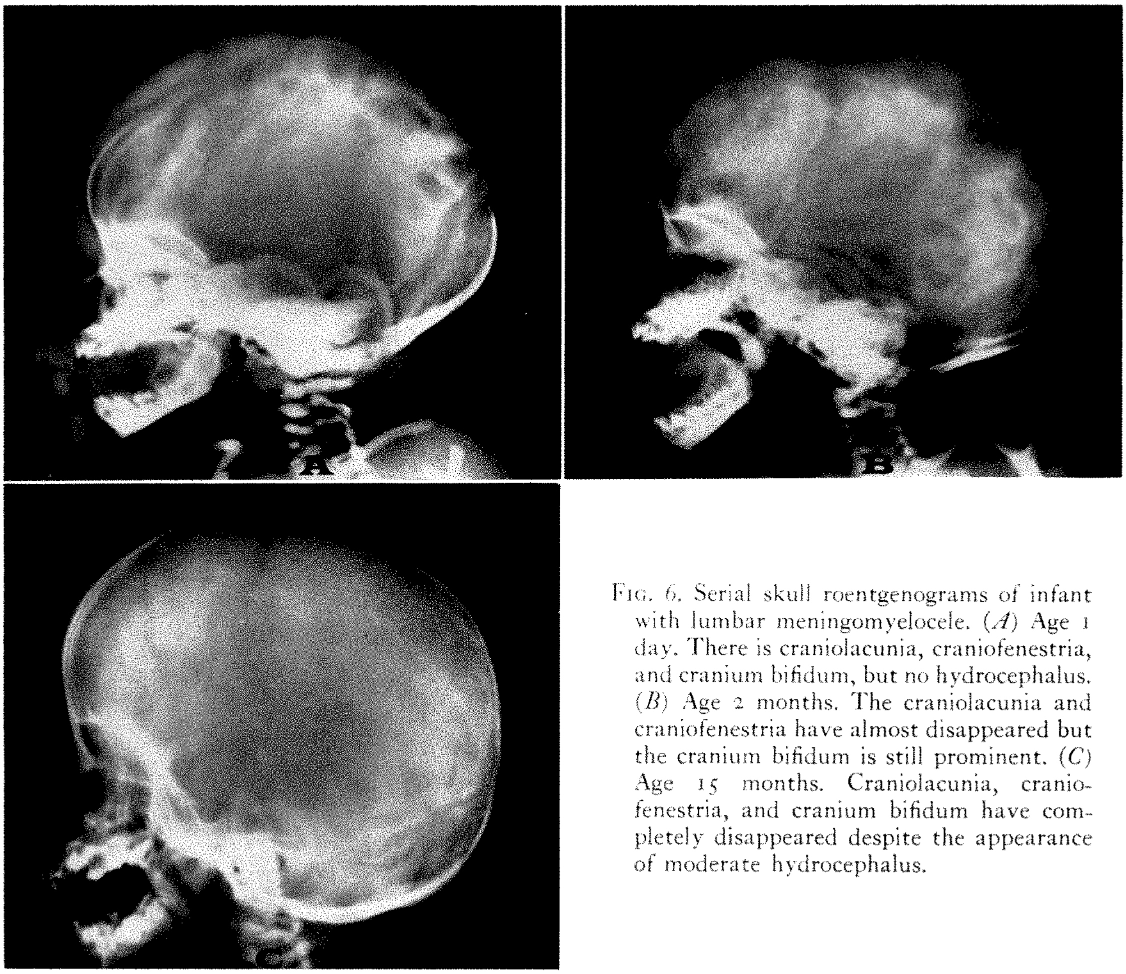

FIG. 6. Serial skull roentgenograms of infant with lumbar meningomyelocele. (*A*) Age 1 day. There is craniolacunia, craniofenestria, and cranium bifidum, but no hydrocephalus. (*B*) Age 2 months. The craniolacunia and craniofenestria have almost disappeared but the cranium bifidum is still prominent. (*C*) Age 15 months. Craniolacunia, craniofenestria, and cranium bifidum have completely disappeared despite the appearance of moderate hydrocephalus.

below the age of 3 months had it, and all those without it were over this age. Comparing the two groups would represent selection of patients in a manner that would produce an invalid conclusion. Many patients in the older age group survived the hazards of infection which are not related to the presence or absence of craniolacunia. It is also a virtual certainty that many of these older patients had craniolacunia which disappeared by the time the skull examinations were done.

A comparison was made of the patients with marked, moderate, and mild craniolacunia. No relationship was found between the severity of the craniolacunia and the death rate. Neither was there any difference in the incidence of anomalies of other systems, degree of neurogenic involvement, and rate of disappearance of the craniolacunia.

Hydrocephalus did not occur in greater frequency in those patients with marked craniolacunia than in those with moderate and mild degrees. The incidence of hydrocephalus was 58 per cent in the total group of 179 patients; it was the same in those with and without roentgenographic evidence of craniolacunia.

DISCUSSION

The terms "craniolacunia" and "Lückenschädel" are used generally and loosely in practice and in the literature[5] to describe radiolucent areas in the skull. The findings reported in this study indicate that they should be strictly reserved for a very definite abnormality with characteristic pathologic and roentgenologic features which distinguish it from lucent areas of other conditions. The features which characterize craniolacunia and permit an accurate identification of it are: (1) presence at birth; (2) association with meningomyelocele and encephalocele; (3) disappearance within 1 to 3 months; (4) defects in the inner table and diploe; (5) complete defects (craniofenestria) commonly occurring with it; (6) frequent association with underossification of the skull bones (cranium bifidum); and (7) localization to the parietal, frontal, and occipital bones in this order of frequency.

It is not possible to draw firm conclusions from this study relative to etiology. However, two distinct impressions were formed: (1) craniolacunia appears to be a developmental defect in which there is faulty ossification of the primitive membranous cranial vault, and (2) craniolacunia is not caused by increased intracranial pressure.

Faulty ossification of the skull bones as the result of a developmental defect was suggested as the cause of craniolacunia by Hartley and Burnett[2] and Rothbart.[6] This theory is supported by the facts that craniolacunia disappears within 1 to 3 months after birth and decreased ossification of the bones along the sutures is an invariably associated finding. Severe hypo-ossification of the adjacent margins of the bones results in cranium bifidum which takes longer to disappear than craniolacunia and craniofenestria. It is suggested that all are due to deficient ossification, cranium bifidum being the more severe involvement of the suture's margins, whereas craniolacunia and craniofenestria are the less severe involvements within the substance of partially formed bone. Cranium bifidum, therefore, would be a sutural craniofenestria. There is no indication, however, that cranium bifidum passes through a craniolacunia or craniofenestria stage as it disappears. It is possible that such a stage was missed because of the timing of the follow-up examinations.

Hydrocephalus, or increased intracranial pressure during intrauterine life, has been mentioned as a theoretic cause of craniolacunia.[4,8] Hydrocephalus was evident at birth in only 2 of our patients with craniolacunia and in only 22 per cent by the age of 2 weeks. Craniolacunia was always present at birth and its presence had no relationship to the development of hydrocephalus. The fact that craniolacunia disappeared as hydrocephalus developed is even more convincing evidence that it is not caused by increased pressure (Fig. 6, *A*, *B* and *C*).

It seems reasonable to extend the classification of skull defects as suggested by van Waalwijk van Doorn and Boet[8] and to define them as follows:

1. *Craniolacunia*—defect of inner table and diploe of bone adjacent to sutures and covered by dura, outer table and periosteum
2. *Craniofenestria*—defect of inner table, diploe and outer table of bone adjacent to sutures and covered by dura and periosteum
3. *Cranium Bifidum*—defect of inner table, diploe and outer table of bone of adjacent suture margins covered by dura and periosteum
4. *Cranial Herniation*—defect of inner table, diploe, outer table, and periosteum of bone in mid-line, allowing a meningoencephalocele

The classification of cranial defects emphasizes the developmental nature of craniolacunia and the type of defect in the bone as shown by pathologic and roentgenologic studies. It leaves no room for the other conditions erroneously diagnosed as craniolacunia in which there is no true bony defect. It is interesting that the defect through which an encephalocele herniates does not disappear in the manner that craniolacunia, craniofenestria, and cranium bifidum do. This is consistent with the observation that the periosteum is lacking with this defect.

The true incidence of craniolacunia will not be known until a larger group of patients are examined roentgenologically in the neonatal period. It seems likely that an incidence of 100 per cent will be approached if the criteria for the diagnosis of craniolacunia are satisfied.

The association of craniolacunia with meningocele and encephalocele seems consistent. An overwhelming majority of the patients will have spinal meningomyelocele.

SUMMARY

1. The roentgen appearance and differential diagnosis of craniolacunia are discussed.

2. Craniolacunia was noted in all patients with meningocele and/or encephalocele who had skull roentgenograms prior to the age of 3 months.

3. All patients with craniolacunia had a meningomyelocele and/or encephalocele.

4. Craniolacunia disappears within 1 to 3 months.

5. Craniolacunia appears to have no prognostic significance.

6. Hydrocephalus has no influence on the presence and course of craniolacunia.

7. Criteria for the diagnosis of craniolacunia are listed.

8. A classification of cranial defects is presented.

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"FLOATING TEETH" IN A FAMILIAL DISEASE ASSOCIATED WITH DYSPROTEINEMIA THAT IS NOT HAND-SCHÜLLER-CHRISTIAN DISEASE*

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THE roentgen observation of "floating teeth" has been considered pathognomonic of Hand-Schüller-Christian disease. The occurrence of "floating teeth" in an unusual disease entity associated with familial dysgammaglobulinemia is the basis of this case presentation.

REPORT OF A CASE

R.M.B., a 14 year old Negro girl was admitted to Menorah Medical Center on August 8, 1960, because of swollen gums and loose teeth. The history of raw gums dated back to infancy. At the age of 1 year, she was treated successfully with antibiotics for a whitish exudate which covered the gums. At the age of 4 years, all temporary teeth were lost. The gums healed, remained swollen, reddish, but not tender. The exact dates for permanent teeth eruption could not be obtained.

The patient appeared healthy. The swelling of the gums gave the face a "moon-shaped" appearance. There was erythema and hypertrophy of all gingival tissues with deformity and looseness of all remaining teeth. The gums were dark red, swollen, nontender and had shredded margins. The teeth were loose. There was moderate anterior cervical lymphadenopathy. A functional Grade II systolic murmur was heard at the apex of the heart. The remainder of the physical examination was normal.

Laboratory data. The erythrocyte count was 3.3 million per cu. mm.; the hemoglobin concentration was 8.0 gm. per cent; the white blood cell count was 6,500 per cu. mm. with neutrophils 1 per cent, lymphocytes 67 per cent, monocytes 20 per cent, and eosinophils 12 per cent. There was hypochromia of the red blood cells. The platelet count was 272,000 per cu. mm. The urine was clear and yellow. The specific gravity was 1.026, the pH was 6; the reaction for protein was 1 plus. The 24 hour urine protein was 0.24 gm. per cent. The urine was negative for Bence Jones protein. The urea nitrogen was 7 mg. per cent, the serum calcium 9.4 mg. per cent, the serum phosphorus 4.8 mg. per cent, the cholesterol 127 mg. per cent, the

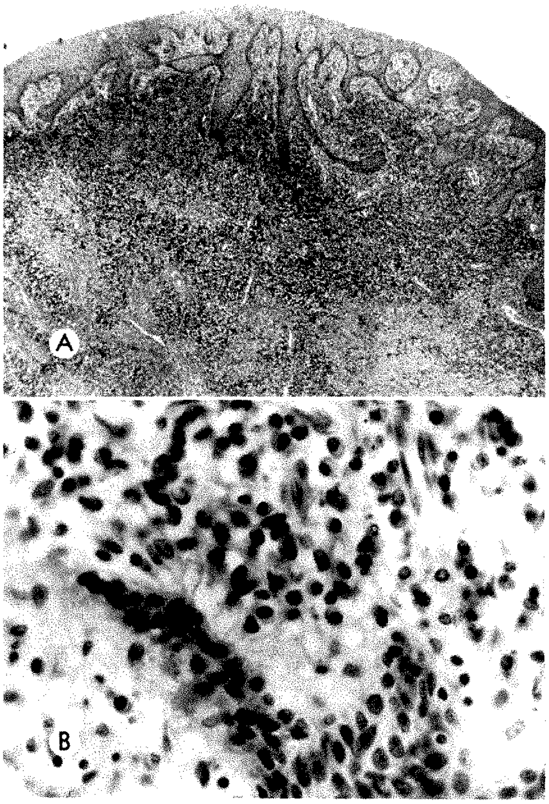

FIG. 1. (*A*) Gingival plasma cell infiltration. (*B*) High power field (×400).

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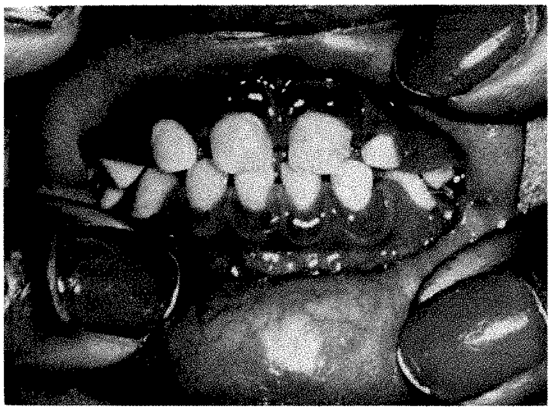

FIG. 2. Gingival hyperplasia in sibling, R. B.

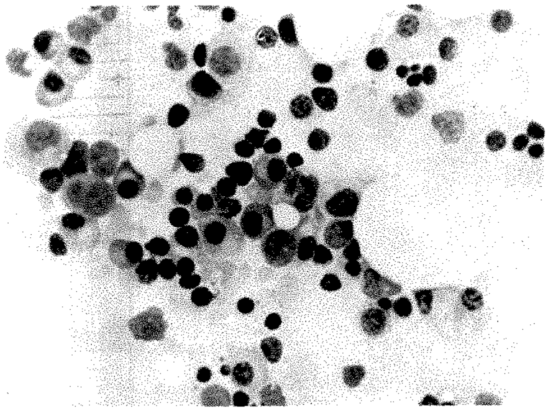

FIG. 4. Plasmacytosis in bone marrow

alkaline phosphatase 1.7 sigma units. The bromsulphalein retention after 45 minutes was 4 per cent. The serum glutamic oxalacetic transaminase (SGOT) was 14 units. The VDRL test was weakly reactive. There was no sickling of the erythrocytes. The hemoglobin electrophoresis was normal. The serum iron was 38 gamma per cent, the unsaturated iron binding capacity was 427 gamma per cent, and the total iron binding capacity was 465 gamma per cent. The prothrombin time was 14 seconds, control 12 seconds. The Ivy bleeding time was 2 minutes 30 seconds, the Lee White coagulation time was 14 minutes. No lupus erythematosus cells were found. The total serum protein was 10.2 gm. per cent. Ultracentrifugation of the serum gamma proteins showed these fractions: S4—3.0 gm. per cent, S7—8.1 gm. per cent, S10—0.332 gm. per cent, and S19—0.476 gm. per cent. Skin tests with tuberculin, coccidiodin, histoplasmin and blastomycin were negative.

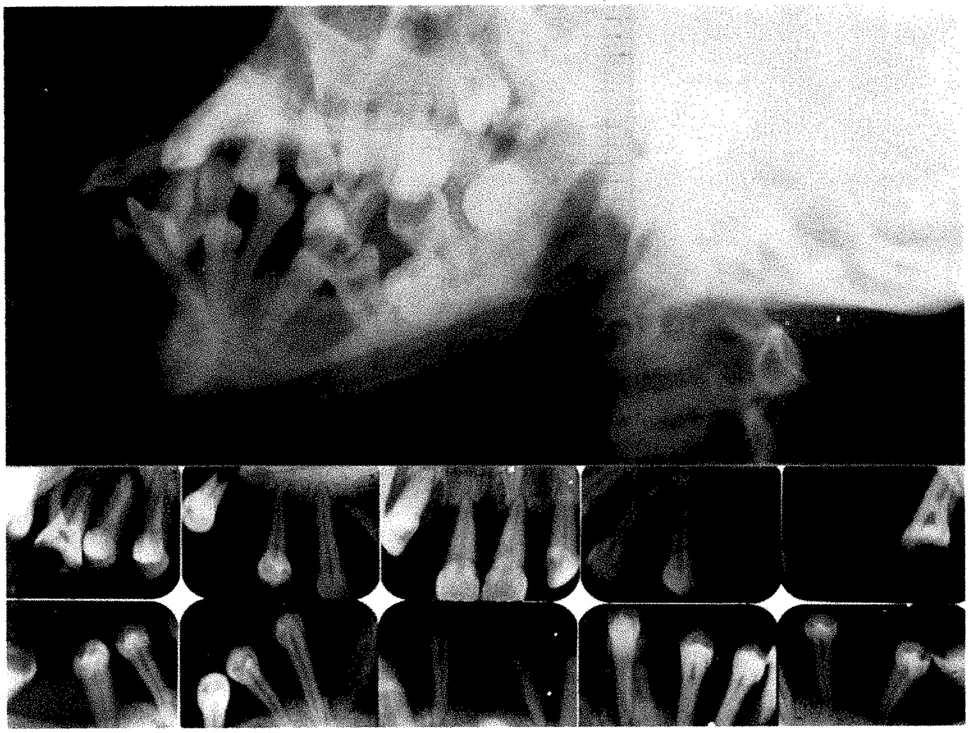

FIG. 3. Replacement of bony alveolus by cellular infiltration, presenting a floating appearance of the teeth.

TABLE I

ESSENTIAL FEATURES OF "B" FAMILY

	White Blood Cell Count and Differential in Per Cent	Serum Proteins Electrophoresis Gm. Per Cent	Bone Marrow	Gingival Hypertrophy	Floating Teeth
C. B., Father	Normal	Normal	Normal	0	0
O.B., Mother	Normal	Normal	Plasmacytosis +	0	0
R.M.B., Aged 14	Neutrophils 1 Lymphocytes 67 Monocytes 20 Eosinophils 12	Total Protein 10.2 Albumin 2.60 Alpha 1 Globulin .44 Alpha 2 Globulin .67 Beta Globulin 2.85 Gamma Globulin 3.63	Plasmacytosis ++++	++++	++++
R.B., Sister Aged 7	Neutrophils 0 Stabs 1 Lymphocytes 59 Monocytes 36 Eosinophils 4	Total Protein 7.2 Albumin 3.05 Alpha 1 Globulin .32 Alpha 2 Globulin .63 Beta Globulin 1.30 Gamma Globulin 1.89	Eosinophilia ++ Plasmacytosis ++	++	0
D.B., Sister Aged 5	Neutrophils 4 Stabs 3 Lymphocytes 62 Monocytes 23 Eosinophils 8	Total Protein 8.3 Albumin 3.3 Alpha 1 Globulin .29 Alpha 2 Globulin .70 Beta Globulin 1.28 Gamma Globulin 2.7	Eosinophilia + Plasmacytosis ++	++	0
R.B., Sister Aged 2	Normal	Normal	Normal	0	0

The bone marrow aspiration was very cellular. There was a marked increase in normal plasma cells and a slight increase in reticulum cells. The punch biopsy of the liver showed minimal mononuclear cellular infiltration in the portal fields and lobules.

Histologic examination of two gingival biopsies (Fig. 1, *A* and *B*) showed massive infiltration of the stroma by normal plasma cells and in a few areas an increase in small lymphocytes.

The patient and family were lost for follow-up examination until March, 1964. In the interim, she had lost all teeth and now wears dentures. The gingival hypertrophy has decreased.

Two sisters of the patient, D. B., aged 5, and R. B., aged 7, also had gingival hyperplasia (Fig. 2). The parents of the patient and the 3 sisters were examined. The essential findings are summarized in Table 1.

DISCUSSION

Sosman,[6] Kennedy,[4] and Gross and Jacox[3] have reported the roentgen manifestations of Hand-Schüller-Christian disease and related them to the abnormal deposition of reticuloendothelial cells in various parts of the body. The classic description of Hand-Schüller-Christian disease is associated with the triad of membranous bone defects, exophthalmus, and diabetes insipidus. Frequently, only one of the features of the triad is present. The diagnosis is made by histologic examination of the bone marrow or biopsy of an affected area demonstrating the classic histiocytic cells.

The oral manifestations that develop are secondary to gingival infiltration by histiocytes, adventitial cells, macrophages, endothelial leukocytes and polyblasts. The migration of these cells about the bony alveoli of the mandible causes erosion of the bone architecture around the teeth. This produces loose dental structures and an erasure of bone which roentgenographically suggest "floating teeth."

The similarity of the roentgen findings in our patient is explained on a comparable pathogenesis. The gingivae are infiltrated massively by plasma cells and in a few areas by small lymphocytes. This infiltration causes the displacement of the normal gingival and bony architecture. The roentgen examination of the mandible and teeth (Fig. 3) demonstrates the replacement of alveolar bone by nonopaque cellular deposition. In some areas, the teeth are devoid completely of any supporting bone structure and, therefore, present the characteristic "floating" appearance.[7]

The hypergammaglobulinemia, marked plasmacytosis of the bone marrow (Fig. 4), familial incidence, anemia and occurrence in a Negro family are features further differentiating this patient from Hand-Schüller-Christian disease. The classic bone marrow of Hand-Schüller-Christian disease shows histiocytic infiltration,[5] but no replacement of normal marrow tissue. Familial occurrence of Hand-Schüller-Christian disease is unknown and the occurrence in Negroes is rare.[2] Thannhauser[8] states that the presence of high serum globulin differentiates multiple myeloma from Hand-Schüller-Christian disease. Avery *et al.*[1] found no consistent chemical abnormality of the blood, and anemia only rarely, in a series of cases of Hand-Schüller-Christian disease.

Further studies on the dysgammaglobulinemia of this family are in progress.

SUMMARY

"Floating teeth" are described in a patient with familial dysgammaglobulinemia. The pathology of the gingival lesion and the differential diagnosis are discussed.

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We are grateful for the fine photography by Mr. Robert Trethewey and to Mrs. Jane Beeler for her role in the microscopy.

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THE ROENTGEN APPEARANCE OF THE HAND AND WRIST IN GONADAL DYSGENESIS*

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GONADAL dysgenesis (Turner's syndrome, gonadal aplasia) is a congenital disorder associated with chromosomal aberrations. Due to newer diagnostic techniques, a more accurate and more frequent diagnosis of this syndrome is now made. Although some of the roentgen manifestations of gonadal dysgenesis, for instance the deformity of the medial tibial condyle, have been described in the medical literature,[5,8,10,11,12] reports concerning the roentgen findings of the hand and wrist in this disease are scarce and incomplete.

Osteoporosis has been described to occur frequently in gonadal dysgenesis. Opinions regarding the bone age differ; some believe that it is normal,[9,14] while others state that it is delayed.[3,4] Anomalies of the fingers and Madelung's deformity have occasionally been noted.[6,9,10,13] Two roentgenographic findings of the hand and wrist which have been described in detail, however, are the metacarpal sign by Archibald, Finby and DeVito[2] and the carpal sign by Kosowicz.[7]

The purpose of the author is to call attention to the roentgenographic findings which previously have not been reported and to discuss the changes found on the roentgenograms of the hand and wrist, their incidence, and diagnostic value (Table I).

MATERIAL AND METHODS

Roentgenograms of the hand and wrist in dorsopalmar view were made of 42 patients with gonadal dysgenesis between the ages of 6 to 51 years. In all of the patients, signs of ovarian hypofunction were present, 39 patients were of short stature and 3 attained normal height after the age of puberty. The diagnosis was confirmed in 18 patients by laparotomy which revealed typical fibrous whitish streaks instead of ovaries in the broad ligaments. In the remaining cases the diagnosis was supported by chromatin or chromosome studies. A negative chromatin pattern in buccal mucosa smears was found in 26 patients. Chromosome counts of the peripheral blood were obtained in 10 patients; these revealed an XO pattern in 7 patients and a mosaic pattern XO/XX in the 3 remaining patients.

In order to obtain reproducible and precise data on roentgenograms of the hands, the bones of the fourth finger of each hand were measured as follows: length and minimum width of the phalanges and metacarpals, and in the distal phalanges, the diameter of the tuft. The bones of the fourth finger were chosen because the changes, although widespread, were best visible in them.

TABLE I

INCIDENCE OF ROENTGEN CHANGES OF THE HAND AND WRIST IN 42 PATIENTS WITH GONADAL DYSGENESIS

Roentgen Findings	Gonadal Dysgenesis (per cent)	Control Females (per cent)
Drumstick distal phalanges	26	1
Slender shafts	33	5
Convex metaphyses	24	6
Flattening of epiphyses	12	1
Phalanges preponderance	57	10
Brachyphalangia and brachymetacarpia	23	6
Metacarpal sign	60	13
Carpal sign	55	6
Coarse trabeculation	62	2
Delayed epiphyseal fusion in patients over 15 yr.	~80	6
Madelung's deformity and protruding ulna	12	1
Soft tissue changes and nail anomalies	25	8

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Comparative measurements of these bones were made on roentgenograms of 100 control subjects of various ages. The length-to-width ratios of the phalanges and metacarpals were estimated both in normal subjects and in patients with gonadal dysgenesis. The data were subjected to statistical analysis and the results which differed from the normal values by more than 2 standard deviations were considered abnormal. In addition, roentgenograms of the hands in 146 patients with stunted growth of various origin were checked for the presence of the signs described below as characteristic of gonadal dysgenesis.

ROENTGEN FINDINGS

THE BONE AGE

The determination of the bone age was based on 128 roentgenograms obtained in 42 patients. In 24 patients it was possible to check the bone age for a period from 3 to 10 years. It was noted that ossification centers appeared at the normal time in all patients aged 5 to 13 years. The bone age corresponded closely to the chronologic age until the patients reached the age of 13 years. During the next few years, bone maturation did not usually advance further, which indicates that there was no epiphyseal fusion in the majority of patients at the proper time. Thus, the bone age in patients aged 14 to 20 years corresponded to that of 13, 14 or 15 years. In 28 patients the delay in epiphyseal fusion was 3 to 6 years, exceptionally up to 10 years. In only 4 patients did the epiphyses fuse with the shafts during the normal age period. In 4 patients over 27 years of age, the epiphyses had already fused to the shafts, and in the remaining patients previous hormonal treatment could have accelerated the fusion; therefore, the roentgenograms of these patients were not taken into consideration.

The above findings were in agreement with those of my earlier studies based on a smaller group of patients,[6] as well as with the studies by Acheson and Zampa.[1]

THE DISTAL PHALANGES

In 11 cases of gonadal dysgenesis, the distal phalanges were of a peculiar shape, differing markedly from those of normal subjects and patients with other growth disturbances. The tuft was round, enlarged and of decreased density; the shaft was elongated, narrowed in the middle, and both sides of the shaft were biconcave; the base was narrow thus contrasting with the ballooned tuft. The term "drumstick" distal phalanx seems to appropriately define this finding. In normal subjects the distal phalanges showed a smaller but quite dense tuft of less regular shape, a stocky shaft with the sides running nearly straight, and a stronger base.

Measurements of the dimensions of the bones confirmed that there is a difference in the shape of the distal phalanges in patients with gonadal dysgenesis and normal subjects. The ratio of the tuft width to the shaft width in normal subjects was 1.3 (standard deviation 0.17). In the 42 patients with gonadal dysgenesis, this ratio was definitely increased above 1.7 in 18 cases. Similarly, estimates of the length-to-width ratio of the shaft in normal subjects showed a mean value of 3.6 (standard deviation 0.4), while in 14 patients with gonadal dysgenesis this ratio was increased, exceeding the normal values by more than 2 standard deviations.

THE MIDDLE AND PROXIMAL PHALANGES AND THE METACARPALS

In many patients with gonadal dysgenesis, the shafts of these bones were slender and narrowed across the middle. The ratios of the shaft length to its minimum width in normal subjects showed the following mean values: in the middle phalanges 3.5 (standard deviation 0.3), in the proximal phalanges 4.6 (standard deviation 0.4), and in the metacarpals 9.1 (standard deviation 1.1). In gonadal dysgenesis abnormally high length-to-width ratios were found: in the middle phalanges in 9 cases, in the proximal phalanges in 14 cases, and in the metacarpals in 2 cases.

Between the ages 15 to 22 years, in patients with gonadal dysgenesis the epiphyses of the phalanges as well as of the metacarpals became wider than the adjacent metaphyses and showed tiny projections toward the metaphyses on both margins. After fusion of the epiphyses to their shafts, no abnormalities were evident.

In 5 patients, the heads of the fourth and third metacarpals were flattened; *i.e.*, the articular facets of the epiphyses were definitely less convex than in normal. Shortening of some of the phalanges (brachyphalangia) or metacarpals (brachymetacarpia) was noted in 9 patients; in 1 case all the metacarpals were shortened. The shortening of the phalanges or metacarpals was usually preceded by bulging of

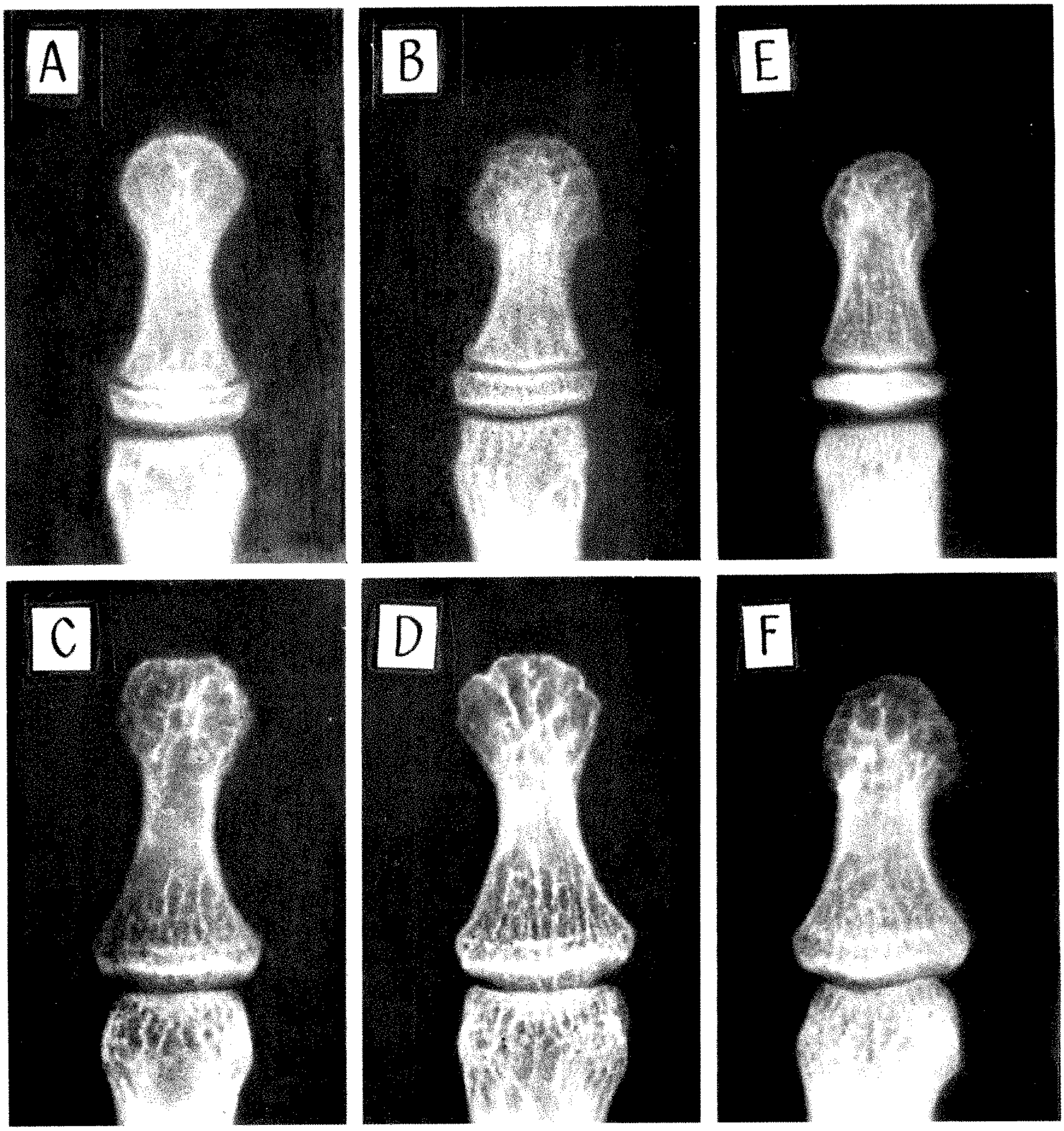

Fig. 1. (*A-D*) Drumstick distal phalanges typical of gonadal dysgenesis as compared to normal bones (*E* and *F*). The distal phalanges of patients with gonadal dysgenesis before and after epiphyseal-diaphyseal fusion have a round and enlarged tuft, constricted and elongated shaft and a narrow base.

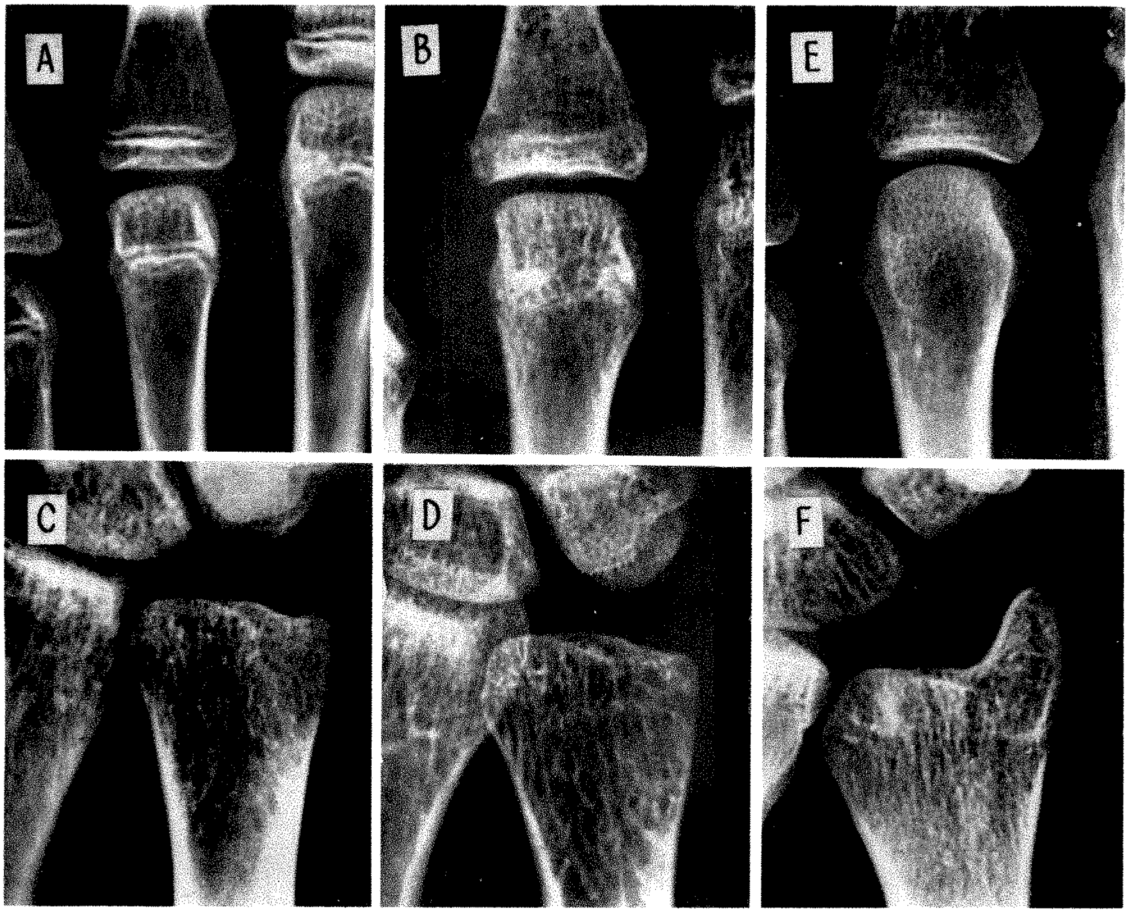

FIG. 2. (*A–D*) Flattening of epiphyses in gonadal dysgenesis. (*A* and *B*) Flattened metacarpal heads. (*C* and *D*) Distal ulnar ends. (*E* and *F*) Normal bones.

the epiphysis of the affected bone toward its shaft and by subsequent premature fusion of the epiphysis to its shaft.

Both hands were checked for the presence of the metacarpal sign as described by Archibald and his associates and illustrated in Figure 5, *A* and *B*. Positive or borderline metacarpal findings were noted 25 times in the left hands and 21 times in the right hands of the patients, whereas in control subjects the incidence of this sign was 13 per cent.

PREPONDERANCE OF THE PHALANGES OVER METACARPALS

A comparison of the length of the metacarpals with the length of the phalanges in a number of cases of gonadal dysgenesis revealed a definite disproportion: a relative shortness of the metacarpals which contrasted to the normal length of the phalanges. This disproportion was present in the bones of all fingers but was best observed on the fourth finger.

Normally, the total length of the distal and proximal phalanges of the fourth finger equals the length of the metacarpal, the standard deviation being 2 mm. Figuratively speaking, the distal and proximal phalanges could be placed in tandem in the metacarpal and, similarly, the distal phalanx could be placed 3 times in tandem in the fourth metacarpal.

There was quite a different situation in the 24 cases of gonadal dysgenesis. In these patients the total length of the distal and proximal phalanges exceeded the length of the fourth metacarpal by 3 or more milli-

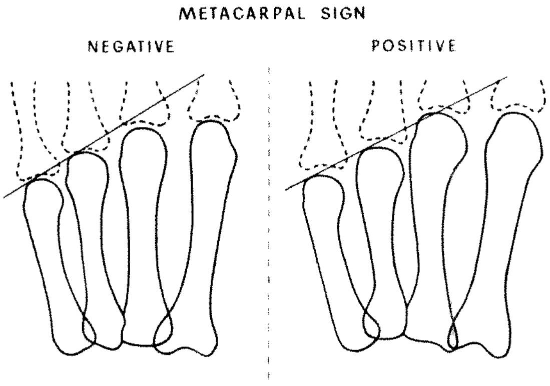

Fig. 3. Line drawing illustrating the metacarpal sign. In the majority of patients with gonadal dysgenesis, a tangent touching the outlines of the fifth and fourth metacarpal heads runs through or touches the head of the third metacarpal. In nearly 90 per cent of normal subjects, this tangent runs above the head of the third metacarpal.

meters. Thus the distal and proximal phalanges could not be placed in tandem in the metacarpal. Likewise, in 16 patients with gonadal dysgenesis the distal phalanx of the fourth finger was too long to be placed 3 times in tandem in the fourth metacarpal. It seems appropriate to call this specific disproportion between the length of the phalanges and metacarpals the "preponderance of the phalanges over metacarpals."

THE WRIST AND ENDS OF THE FOREARM BONES

Abnormally shaped bones of the proximal carpal row were noted often in gonadal dysgenesis. These bones did not form a slight arch as is normal but were angular. This roentgenographic finding, called the carpal sign,[7] is best evaluated on roentgenograms of the wrist and hand taken in the neutral position when 2 tangents are drawn, the first one touching the proximal outline of the scaphoid and lunate bones, and the second one, touching the triquetral and lunate bones. The intersection of the 2 tangents forms an angle, called the carpal angle, which in normal subjects measures 131.5° (standard deviation 7.2°). In 23 patients with gonadal dysgenesis, the car-

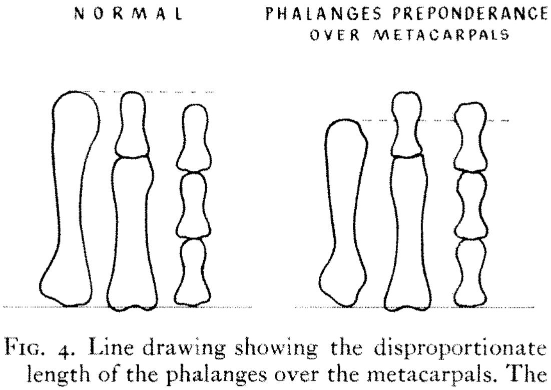

Fig. 4. Line drawing showing the disproportionate length of the phalanges over the metacarpals. The usual proportions of these bones in a normal subject are shown for comparison.

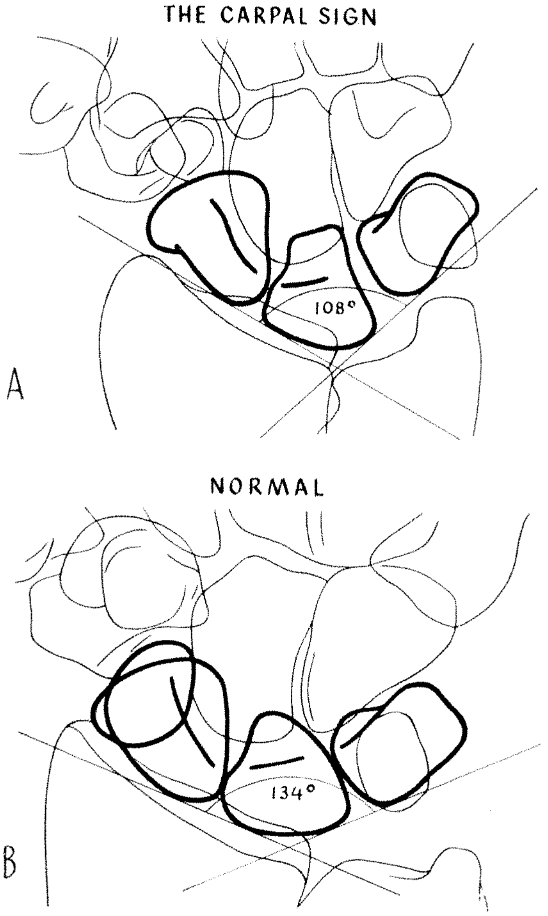

Fig. 5. (*A*) Line drawing of the wrist illustrating the positive carpal sign in a patient with gonadal dysgenesis. The bones of the proximal carpal row are angularly arranged, the carpal angle being 108°. (*B*) In normal subjects the bones of the proximal carpal row form a slight arch. Two lines drawn tangentially to the contours of these bones form a normal carpal angle of 134°.

pal angle was definitely reduced, ranging from 102 to 117°, thus being smaller by more than 2 standard deviations from normal. In other patients with gonadal dysgenesis, the carpal angle was slightly decreased, ranging from 118 to 131°, but never exceeding the mean value of this angle in normal subjects.

Another finding, a coarse trabecular structure, was demonstrable in 26 patients. This coarse trabeculation was most clearly seen in the wrist, next in the bases and heads of the metacarpals and phalanges, and then in the distal radial epiphysis. Both changes, the positive carpal sign and the coarse trabecular pattern, were already evident in patients 6 to 10 years old.

In 10 patients the distal radial metaphysis was convex toward the epiphysis. The adjacent epiphyseal plate did not run straight as is normal but was arched, and the distal radial epiphysis was moulded close to the convex metaphysis, being narrowed in the mid portion and expanding on both sides toward the metaphysis.

There was typical Madelung's deformity in 2 patients. In addition, in 5 other cases of gonadal dysgenesis, the distal radial epiphysis fused irregularly with its shaft, first on the ulnar side and some years later on the radial side. In these cases after fusion of the epiphysis to its shaft, the radiocarpal articular facet became more steep than is normal.

In 5 patients the distal ulnar end appeared flattened since the styloid process of the ulna had not developed. In 3 other patients the distal end of the ulna protruded distalwards more than is usual.

SOFT TISSUE CHANGES

Some thickening of the soft tissues surrounding the bones of the fingers was noticed in 8 patients. This thickening, more prominent about the middle of the phalangeal shafts and less pronounced at the interphalangeal joints, was in contrast to the slenderness of the shafts of the phalanges. Physical examination of these patients showed edema of the dorsa of the fingers. Occasionally, roentgenograms revealed bulging of the tip of the fourth finger or curving of the fingers.

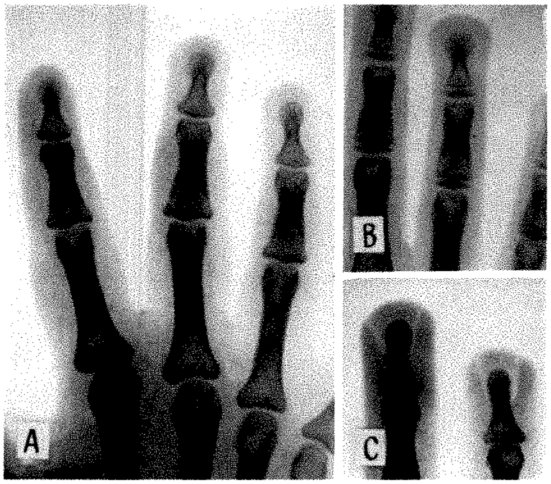

Fig. 6. Nonosseous changes sometimes seen in gonadal dysgenesis. (*A*) Thickening of soft tissues of the fingers not involving the periarticular areas; (*B*) bulging of the finger tip; and (*C*) narrowing of the nails.

Changes of the nails, *i.e.*, narrowing or shortening of the nails, were sometimes visualized on roentgenograms but were most often noted on physical examination.

COMMENT

OTHER GROWTH DISORDERS

Roentgenograms of the hand in patients with other growth aberrations very rarely showed findings typical of gonadal dysgenesis. In primordial dwarfs the bone age was found to be normal and all the bones of the hand were of proportionally decreased dimensions without evidence of any other changes. Roentgenograms of children with hypothyroidism and pituitary dwarfism showed that the bone age was definitely delayed. This is in contrast to the normal bone age of children with gonadal dysgenesis. In patients over the age of 18 years, delay in epiphyseal fusion was a common finding in pituitary dwarfs as well as in patients with gonadal dysgenesis; however, a coarse trabecular structure, drumstick distal phalanges, disproportionate length of the phalanges in comparison to the

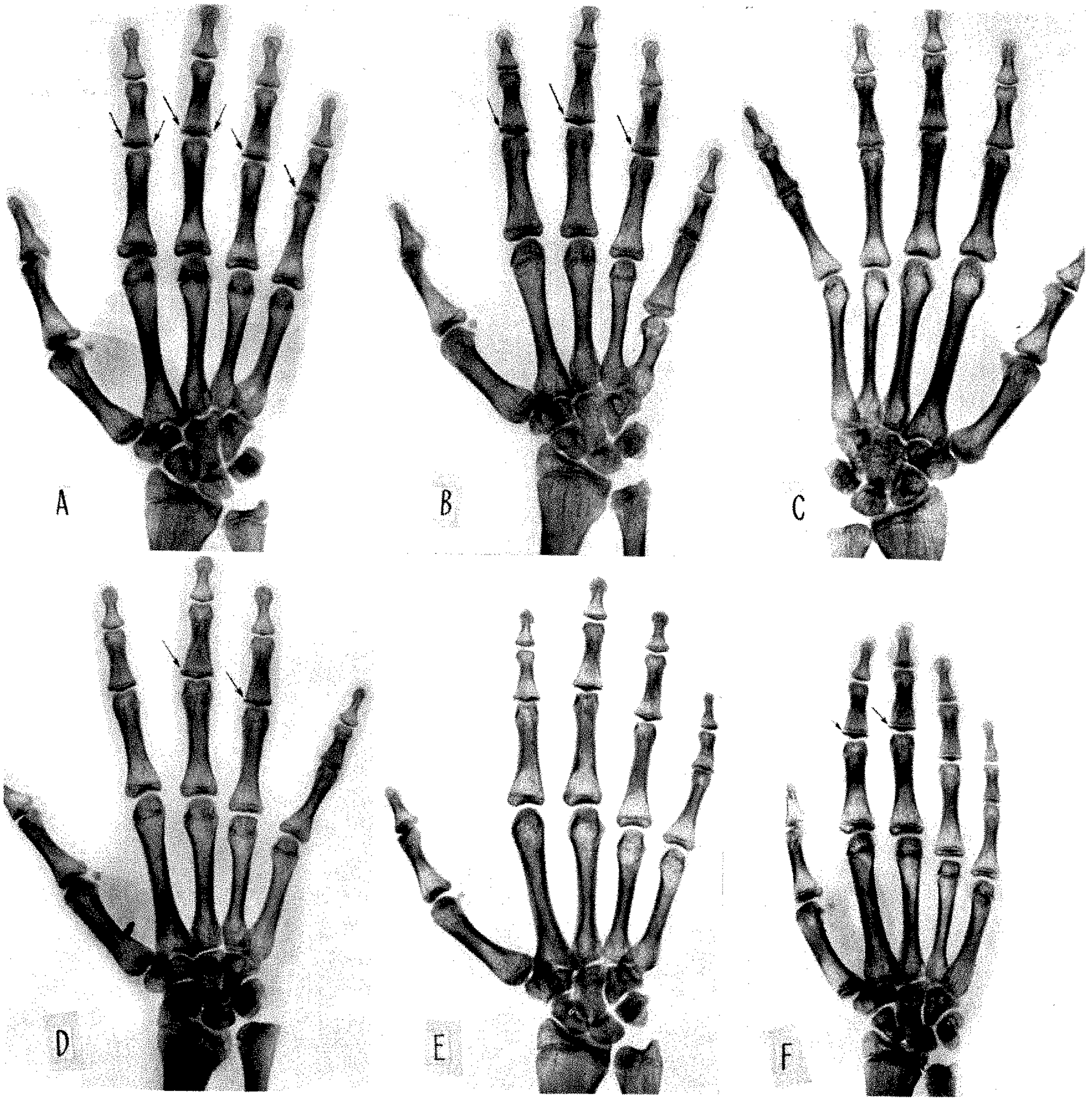

Fig. 7. (*A*) 20 years; (*B*) 18 years; (*C*) 30 years; (*D*) 19 years; (*E*) 26 years; and (*F*) 15 years old. Roentgenograms of the hand and wrist in 6 cases of gonadal dysgenesis showing the following findings: drumstick distal phalanges in *A*, *B*, *D* and *F*; marginal projections of widened epiphyses toward their shafts (arrows) in *A*, *B*, *D* and *F*; phalanges preponderance over metacarpals in *A*, *D*, *E* and *F*; positive metacarpal sign in *C*, *D* and *F*; flattening of epiphyses of the fourth metacarpal or ulnar end in *C*, *D* and *F*; slenderness of the shafts of some phalanges in *A*, *B*, *C* and *F*; positive carpal sign in *A*, *B*, *D* and *E*; coarse trabeculation, especially of the wrist, in *B*, *C* and *F*; delayed epiphyseal-diaphyseal fusion in *A*, *B* and *E*; convex radial metaphysis with corresponding narrowing of the epiphysis in *A*, *B*, *D* and *F*; and shortening of the fifth middle phalanx or fifth metacarpal in *B*, *D*, *E* and *F*.

metacarpals, flattening of epiphyses, convex metaphyses, and slender shafts were not seen in pituitary dwarfs.

SUMMARY AND CONCLUSIONS

Roentgenograms of the hand and wrist in 42 patients with gonadal dysgenesis (Turner's syndrome) demonstrated findings which when present in combination may be diagnostic of the disease. These are:

1. A normal bone age in patients up to the age of 13 years and a delay in epiphys-

eal fusion in patients over this age.

2. A coarse trabecular structure especially in the carpal bones and in the heads and bases of the metacarpals and phalanges.

3. Peculiarly shaped distal phalanges with a round and enlarged tuft, elongated and constricted shaft and a narrow base (drumstick distal phalanges).

4. Slender shafts, *i.e.*, an increased length-to-width ratio of the long bones.

5. The metacarpal sign.

6. The preponderance of the phalanges over metacarpals, *i.e.*, a relative lengthening of the phalanges as compared to the stunted metacarpals.

7. The carpal sign.

8. Convex metaphyses with adaptive changes of epiphyses which show tiny marginal projections toward the shafts.

9. A shortening of some phalanges or metacarpals preceded by bulging and premature fusion of the epiphyses to their shafts.

10. A flattening of the epiphyses, mainly of the metacarpal heads and the distal end of the ulna.

11. Soft tissue changes as evidenced by thickened fingers and nail anomalies.

These roentgen findings were noted frequently in patients with gonadal dysgenesis. On the other hand, they were infrequently observed in healthy subjects as well as in patients with other growth disturbances.

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BROAD THUMBS AND TOES, AND UNUSUAL FACIAL FEATURES*

A PROBABLE MENTAL RETARDATION SYNDROME

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IN AN earlier publication,[2] the authors reported 7 patients with mental and motor retardation, broad thumbs and great toes, facial and other abnormalities, and suggested the possibility of these features representing a previously undescribed syndrome. Due to the limited number of the cases, we brought up the possibility of a fortuitous association of unrelated clinical findings. However, since the publication of that paper, we have personally seen 3 new cases and received information regarding over 24 others from our colleagues in the United States, Europe, and Japan.

Six new cases are presented here and the clinical and roentgenographic manifestations are briefly discussed. Cases 11 and 12 have been reported to us by Dr. Stanley W. Wright, Chief of Research, Pacific State Hospital, Pomona, California, and Case 13 by Dr. T. C. Papermaster, Pediatric Consultant, State of Minnesota Child Development Center, Fergus Falls, Minnesota.

The major and more common clinical and roentgenographic manifestations of the previously reported cases (Case 1 to 7) and the 6 new cases (Case 8 to 13) are summarized in Table 1. Figures 1 through 3 demonstrate the foramen magnum, and hands and feet of the 6 new cases. Other significant points in the history of the new cases appear below.

It may be mentioned that 6 additional cases have been reported recently by Coffin.[1]

REPORT OF NEW CASES

Case 8. Surgery was performed in the first year of life for patent ductus arteriosus, at 2½ years of age for excision of the medial portion of the right great toe, and at 7 years for removal of a composite odontoma of the right maxilla and multiple carious teeth.

Case 9. Spina bifida with meningomyelocele was present at birth and was repaired at 2 days of age. Persistent lacrimation of the right eye has been noted since birth and diagnosed as being due to a congenital obstruction of the nasolacrimal duct. Excretory urography and cystoscopy indicated apparent absence of the right kidney. The patient lacks normal urine and fecal continence. Combined pneumoventriculography was performed in another institution at about 20 months of age and revealed abnormal sulci of each hemisphere and indicated "cerebral dysgenesis." The patient's teeth are in "poor condition" and covered with calculus.

Case 10 demonstrates rather marked hyperextensibility of the thumbs and hips, has very deep creases on the plantar surface of the foot in the first interdigital space, and has had 2 episodes of pyelonephritis.

Case 11 had incomplete descent of testes by history, but at the age of 15 years, 9 months showed complete descent. There was scant straight pubic hair and no beard or axillary hair. There was malocclusion with overriding of the upper jaw and irregular placement of teeth. He had a peculiar stiff, knock-kneed gait.

Case 12 has a coloboma of the inferior medial part of the fundus of the right eye. At the age of 16 she shows early breast development; has had one menstrual period but has no axillary or pubic hair. She, too, has a knock-kneed gait.

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Table I

CLINICAL AND ROENTGENOGRAPHIC FINDINGS OF 13 PATIENTS WITH THE SYNDROME

Case No.	1	2	3	4	5	6	7	8	9	10	11	12	13	Total
A. Clinical Features Age (in years)	$3\frac{1}{2}$	$7\frac{1}{2}$	3	$8\frac{1}{2}$	$4\frac{9}{12}$	$8\frac{1}{2}$	$7\frac{10}{12}$	$7\frac{1}{12}$	$4\frac{10}{12}$	5	15	16	$6\frac{9}{12}$	
Sex	F	M	M	F	M	M	M	F	M	F	M	F	M	
Height	LT3PC	LT3PC	10PC	LT3PC	25PC	25PC	3PC	3PC	LT3PC	25–50PC	LT3PC	LT3PC	3PC	
Weight	LT3PC	25–50PC	LT3PC	3PC	50PC	50PC	25PC	25–50PC	LT3PC	3PC	LT3PC	3PC	50–75PC	
Head Circumference	LT3PC	10–25PC	LT3PC	LT3PC	3–10PC	3PC	LT3PC	LT3PC	LT10PC	LT10PC	LT10PC	LT10PC	10PC	
Development Retardation	+	+	+	+	+	+	+	+	+	+	+	+	+	13
Intelligence Quotient	38	48	50	17	62	80	32	56	very low	65–75	24	45	20	
Broad Thumbs and Great Toes	+	+	+	+	+	+	+	+	+	+	+	+	+	13
Highly Arched Palate	+	+	+	+	+	+	+	+	+	+	+	+	+	13
Beaked Nose	+	+		+		+	+	+	+		+	+	+	10
Eye Abnormalities Exotropia or Exophoria	+	+	+	+	+	+		+	+			+	+	13 10
Refractive Error	+	+	+	+		+						+	+	7
Antimongoloid Slant	+		+	+		+	+	+	+	+	+	+	+	11
Ptosis	+	+						+ ?	+ ?			+		
Epicanthus	+				+			+			+			4
Incompletely Descended Testes	F	+ ?	+ ?	F		+	+ ?	F	+	F		F	+	
B. Roentgenologic Features Broad Thumbs	+	+	+	+	+	+	+	+	+	+	+	+	+	13
Broad Great Toes	+	+	+	+	+	+	+	+	+	+	+	+	+	13
Duplication of Phalanges Thumbs									+				+	2
Great Toes			+		+			+	+		+	+	+	7
Other Broad Distal Phalanges	+	+	+	+	+			+	+	+	+ ?	+ ?	+	
Skeletal Maturation	$1\frac{1}{2}$–$2\frac{1}{2}$	4–7	$1\frac{3}{12}$	$4\frac{2}{12}$	3	7–8	5	3	2	$2\frac{1}{2}$	14	14	4	
Large Foramen Magnum	+	+	+			+		+	+	+	?	?	+	

Note: + = present; M = male; F = female; LT = less than; PC = percentile.

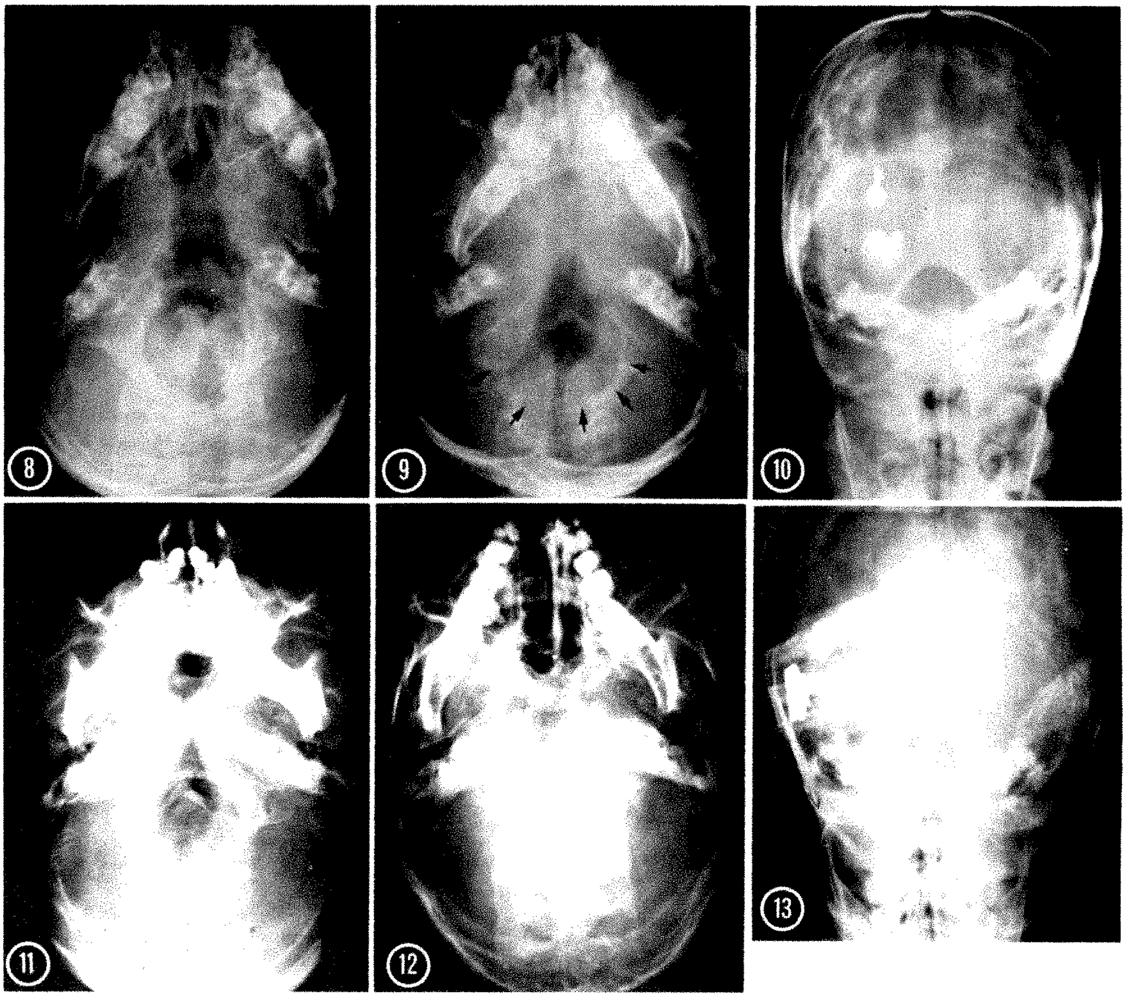

Fig. 1. Different degrees of enlargement of the foramen magnum, particularly in Case 8, 9 and 13, are present.

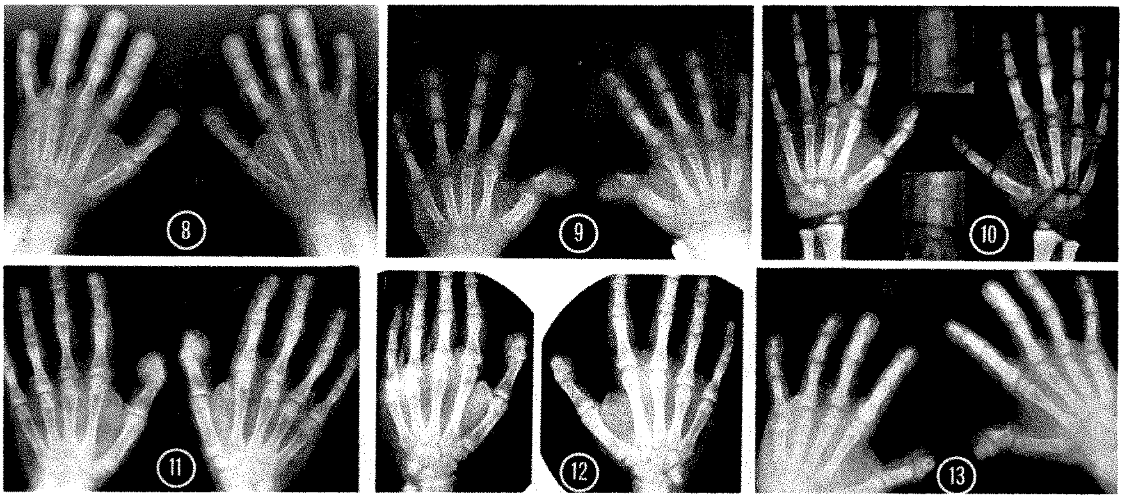

Fig. 2. Broadness of the thumbs and some of the other fingers and abnormal segmentation of some of the phalanges are seen.

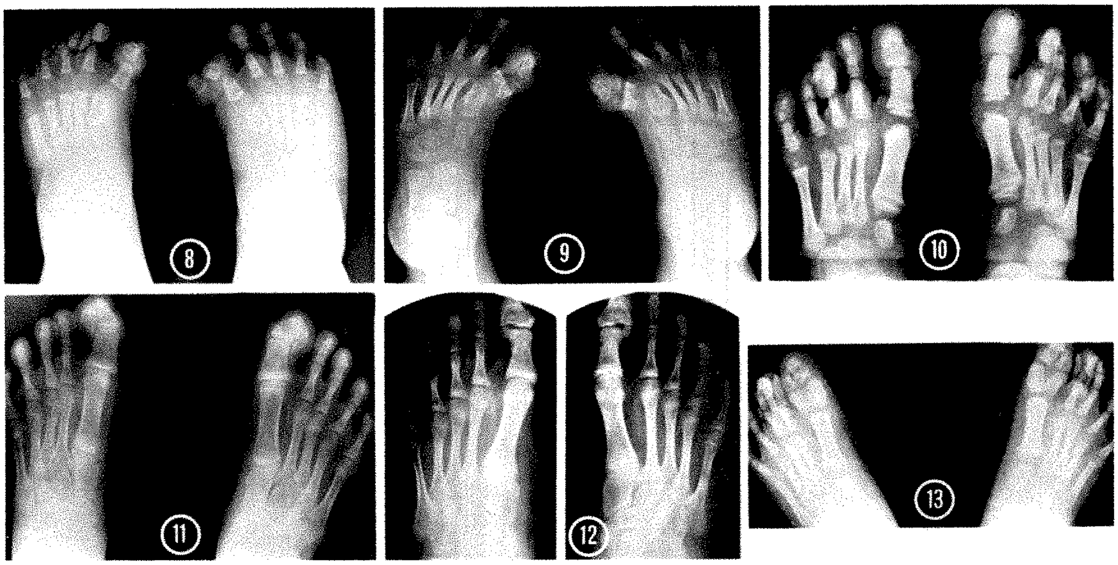

FIG. 3. Broad great toes and abnormal segmentation of several of their phalanges are shown.

CASE 13 has recently had plastic repair with excision of the inner part of duplicated phalanx of the broadened toenail.

COMMENT

Several of these patients had neonatal feeding problems, recurrent respiratory problems and/or allergies in infancy and early childhood.

Electroencephalographic examination was performed in Case 1, 2, 4, 5, 7, 9, 12 and 13, and reported as being diffusely abnormal. In Case 11 it was reported as a normal fast record.

Chromosome analysis in Case 1, 5 and 6 showed apparently normal karyotypes.

DISCUSSION

A review of the clinical and roentgenographic features of these 13 patients revealed two groups of abnormalities; those common to all the cases and those seen in some.

The following findings were common to all the cases: (1) mental and motor retardation; (2) broad thumbs and great toes; (3) a highly arched palate; and (4) eye abnormalities of different types.

The second group of findings present in some and absent in others were: (1) beaked nose; (2) large foramen magnum; (3) delayed closure of the large anterior fontanel; (4) abnormal segmentation with partial duplication of the phalanges of the thumbs and great toes; (5) broad terminal phalanges of other fingers; (6) short stature; (7) skeletal maturation retardation; (8) microcrania; (9) abnormal electroencephalograms without localizing phenomena; (10) neonatal feeding problems; (11) recurrent respiratory problems in infancy and early childhood; (12) allergies; (13) nevus flammeus on forehead or nape of neck; (14) hirsutism; (15) probable functional heart murmur. Case 8 had a patent ductus arteriosus; (16) sternal or rib anomalies; (17) spine anomalies. Case 9 had a myelomeningocele; and (18) apparent absence of a kidney in Case 9, and Case 10 had two episodes of pyelonephritis.

The deformities of the thumbs and great toes have been described by different observers as spatulate, short and stubby, clubbed, flat and wide, and large. The distal phalanx is usually broad and in some cases flat. Similar anomalies may be present in the other distal phalanges; however, the evaluation of the toes other than the great toe is difficult due to normal variation.

The facial appearance in some of our patients (Fig. 4) may remind the examiner of mandibulofacial dysostosis (Fran-

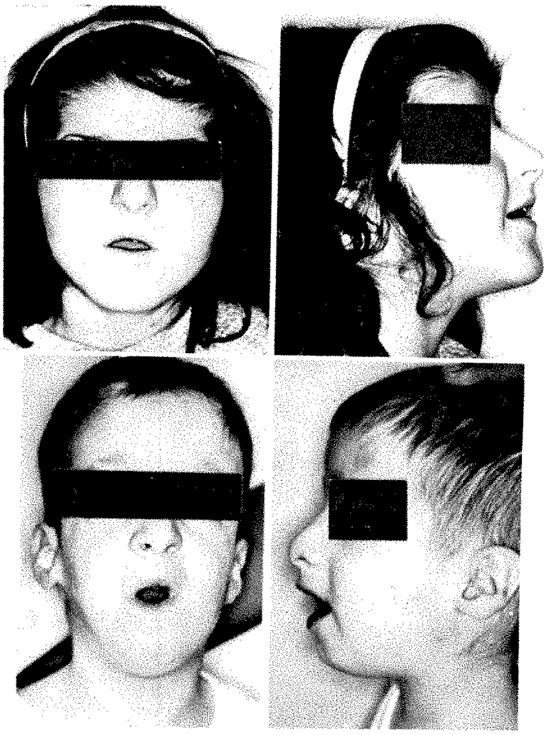

Fig. 4. "Odd" facial features, in particular (antimongoloid slant of the eyes), beaked nose, and microstomia in Case 8 (*top*) and Case 9 (*bottom*) are seen.

ceschetti-Klein or Treacher-Collins syndrome) mainly due to a slight antimongoloid slant of the eyes, the highly arched palate, and the prominent nose. Other features of mandibulofacial dysostosis, *i.e.*, malar and mandibular defects, deafness, "hair tongue," lid colobomas, eyelash defects, and macrostomia, are lacking in our cases. The broad thumbs and toes and mental retardation and other findings listed in Table I are not usually seen in mandibulofacial dysostosis.

This condition has been considered among the possible causes of dwarfism in children.[3]

SUMMARY

Thirteen children with anomalies consisting of broad and short terminal phalanges of the thumbs and great toes, highly arched palate, eye abnormalities, and mental retardation are described. "Odd" facial features, microcrania, growth retardation, incompletely descended testes in the males, large foramen magnum, abnormal segmentation with duplication of the phalanges of the thumbs and great toes, and broad terminal phalanges of other fingers are additional features present in several of these patients.

This, we believe, probably represents a new syndrome. However, more case studies and case reports from other centers are necessary to support our thesis.

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SYMMETRIC BOWING OF THE TERMINAL PHALANGES OF THE FIFTH FINGERS IN A FAMILY (KIRNER'S DEFORMITY)*

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SINCE Kirner[4] in 1927 described the first example of symmetric bowing of the terminal phalanges of the fifth digits of the hands, 17 additional cases have appeared in the literature. This paper reports on 7 cases in 3 generations of one family. It shows the development of bony changes from their beginnings and directs attention to the soft tissue findings.

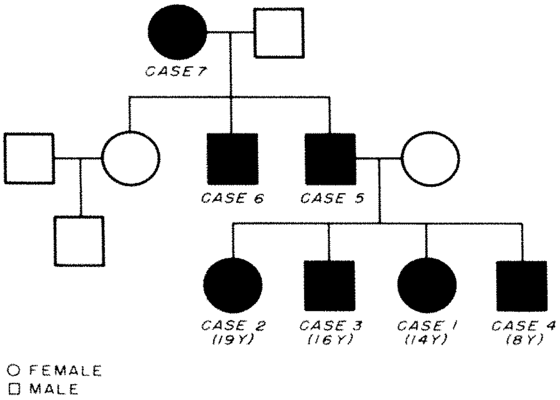

Fig. 1. Solid figures represent individuals with Kirner's deformity. Case 1 is index case. Ages are in parentheses.

MATERIAL

J. K., a 14 year old girl (Case 1), had roentgenograms of her hands made because of acute trauma. Kirner's deformity in both fifth fingers was recognized. Other members of her family were then examined. All 3 of her siblings: 2 brothers, 8 years (Case 4) and 16 years of age (Case 3), respectively; and a sister, 19 years of age (Case 2), had symmetric bowing of the terminal phalanges of their fifth fingers. Their father, aged 56 (Case 5), a paternal uncle, aged 54 (Case 6), and the 83 year old paternal grandmother (Case 7) had similar deformities. The family is of Polish-Czech extraction; its pedigree is shown in Figure 1.

Save for the distal phalanges of their fifth fingers, the bones of the 2 sisters are normal. Their father has bilateral Dupuytren's contractures as well as Kirner's deformity. The health of all has been good except for early poor weight gain in the first patient. Roentgenograms of her hands (Fig. 2, *A* and *B*) when she was 6 and 18 months of age did not show the deformity. Photographs of her hands at the age of 14 years and those of her 19 year old sister (Case 2) showed the soft tissue deformity (Fig. 3, *A* and *B*). The bony lesion in the 14 year old girl (Fig. 4, *A* and *B*) consists of irregular ventrodorsal flattening and bowing dorsad and laterad of the shaft of the terminal phalanx.

A roentgenogram of the hands of the 16 year old brother (Case 3) made when he was $5\frac{1}{2}$ years of age (Fig. 5*A*) demonstrated retardation of maturation; Figure 5, *B* and *C* shows his fifth finger at 16 years of age. The terminal phalanx of the fifth finger was small and straight at $5\frac{1}{2}$ years of age; at 16 years of age it consists of 2 bony parts, an epiphyseal ossification center in its normal location at the base and the primary center for the shaft, which is bowed dorsad and laterad. The epiphyseal ossification center is thick in comparison with its bowed shaft. A flat spur projects distally from its distal edge and fits closely into a slot on the proximal volar face of the shaft. The flat spur appears to serve as a compensating strut to prevent further bowing and forms a mortice and tenon joint with the end of the shaft.

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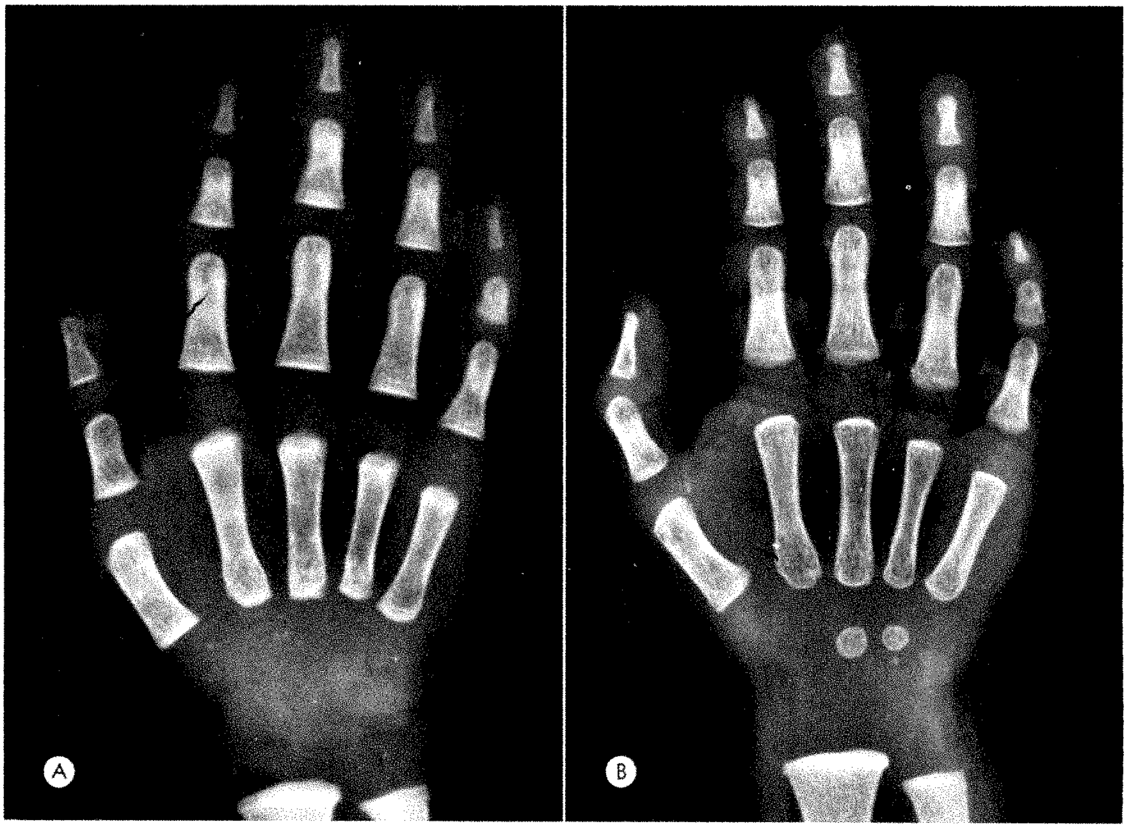

FIG. 2. Roentgenograms of the hands of Case 1 when she was (*A*) 6 and (*B*) 18 months of age. Maturation is retarded but the distal phalanges of the fifth fingers are long, slender and straight.

Roentgenograms of the hands (Fig. 6, *A* and *B*) of the 8 year old brother (Case 4) demonstrate the soft tissue deformity, a globular tip which points toward the thenar eminence. The underlying terminal phalanx does not show bowing.

The hands of the 19 year old girl (Case 2) show a later phase (Fig. 7, *A* and *B*). Fusion of the 2 centers has occurred. The changes in the father's fingers are modified by Dupuytren's contractures (Fig. 8, *A*, *B* and *C*). The bony changes are present in the uncle's hands (Fig. 9, *A* and *B*), although not as marked as the soft tissue deformity.

Roentgenograms of the grandmother were not made, but on physical examination her hands showed globular soft tissue swelling at the tips of both fifth fingers.

REVIEW OF LITERATURE AND DISCUSSION

The 18 cases reported prior to this paper and the present 7 are summarized in Table 1. In all 25 patients the tips of the fifth fingers pointed toward the thenar eminence. The lesions were all painless. The exact age at onset of the clinical deformities or the roentgenographic changes is not known. In 23 the lesions were bilateral; in 2 adequate data for this feature were not given. In 5 reports prior to this one the roentgenograms permitted satisfactory evaluation of bone age; in none of these was bone age retarded but in all of them Kirner's deformity had already developed.

After biopsy of the lesion in one of their patients, a girl 9 years of age, Kaufmann and Taillard[3] concluded that the disorder "primarily affects the metaphysis of the terminal phalanx of the fifth finger." The bone structure was roentgenographically normal in the patients of Hippe[2] and Schmid,[6] 2 and 12 years respectively after recognition of the phalangeal deformities, although the terminal phalanges of the fifth

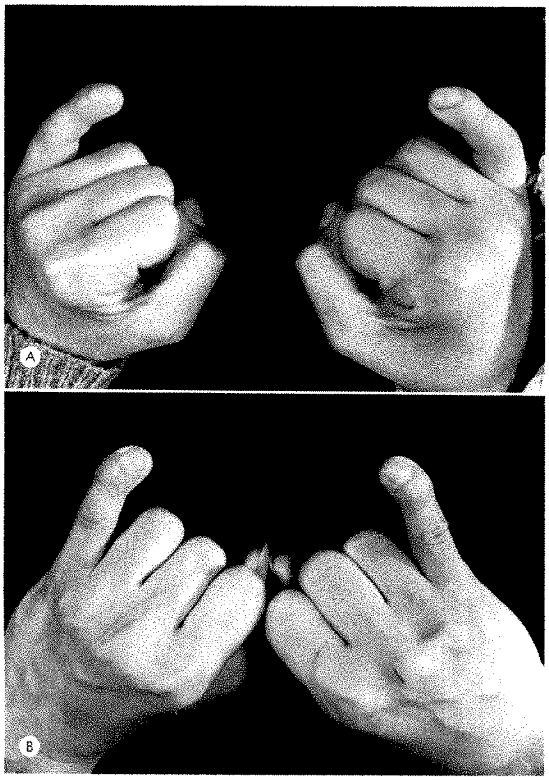

Fig. 3. The hands of (*A*) the 14 year (Case 1) and (*B*) the 19 year (Case 2) old girls show the soft tissue deformity.

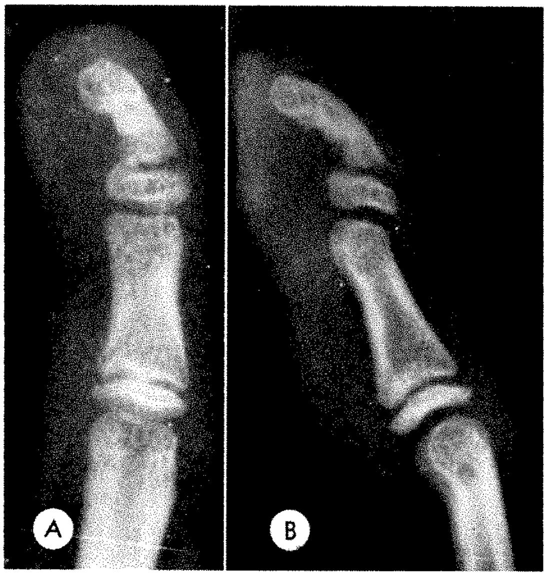

Fig. 4. (*A* and *B*) In the fifth finger of the 14 year old girl (Case 1), the shaft of the terminal phalanx is irregularly flattened and bowed dorsad and laterad; the epiphyseal ossification center does not take part in the bowing.

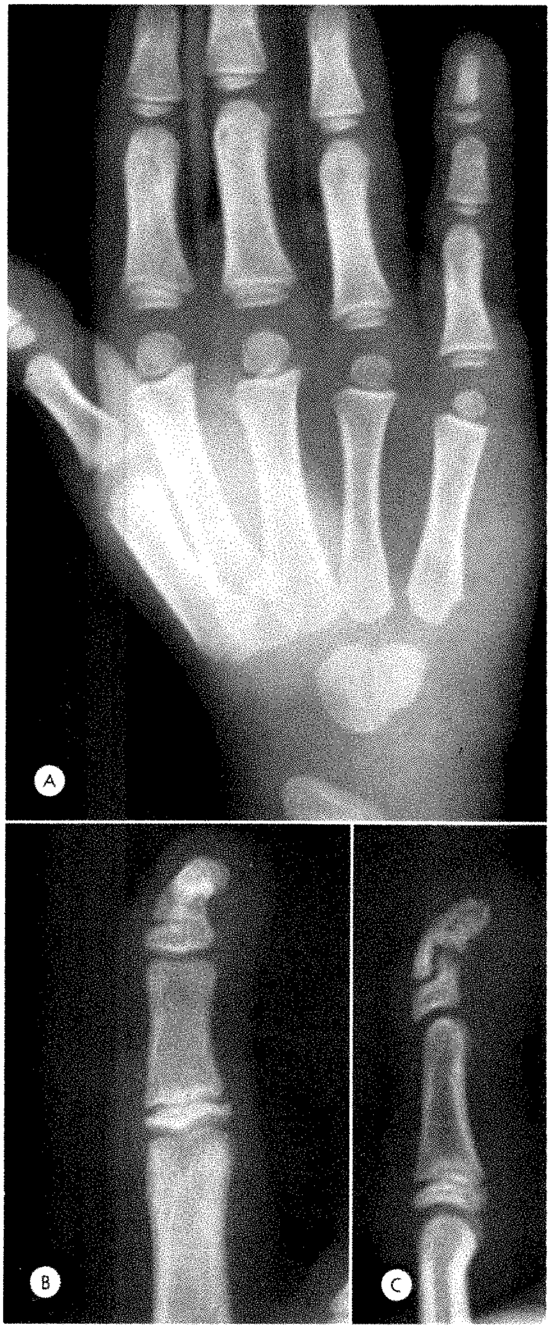

Fig. 5. (*A*) Bone age in the 16 year old boy (Case 3) when his chronologic age was 5½ years lagged by about 2 years. The terminal phalanges of the fifth fingers were small and straight. (*B*) Frontal and (*C*) lateral roentgenograms of the fifth finger. At 16 years of age, the terminal phalanx consists of 2 parts, a thickened epiphyseal ossification center in its normal location and a bowed shaft. A flat spur projects distally from the epiphysis and fits into a slot in the shaft.

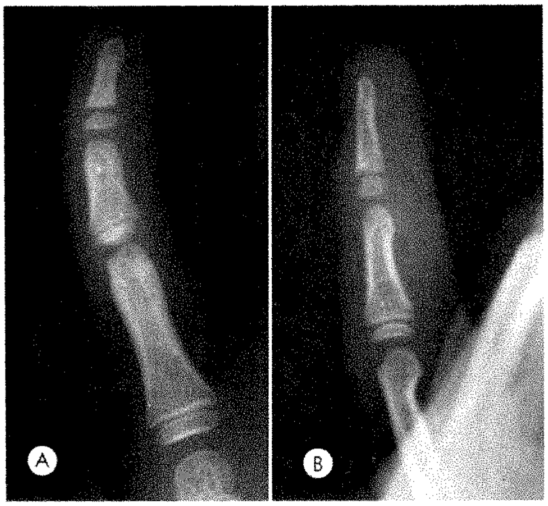

FIG. 6. (*A* and *B*) The tip of the right fifth finger of the 8 year old boy (Case 4) is globular and bent toward the thenar eminence, but the slender terminal phalanx is not bowed. The same finding is present in the left fifth finger.

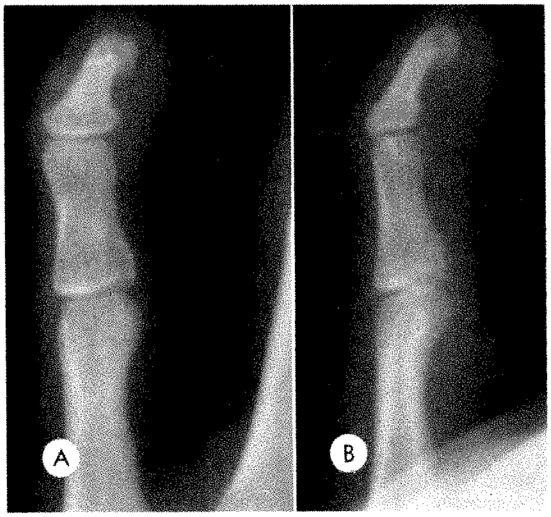

FIG. 7. (*A* and *B*) Bony union has occurred in the hands of the 19 year old girl (Case 2), but the terminal phalanx remains deformed.

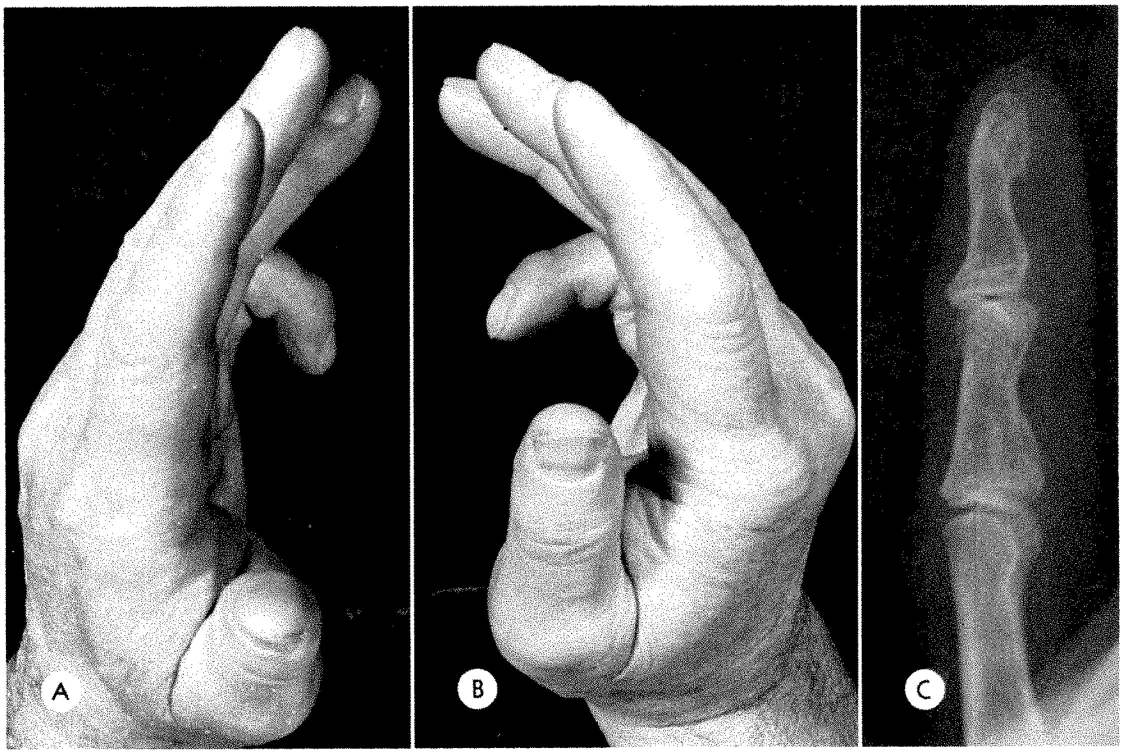

FIG. 8. (*A* and *B*) Photographs of the hands of the 56 year old father (Case 5) shows the deformity and Dupuytren's contracture. (*C*) Roentgenogram shows the deformed terminal phalanx in the father's fifth fingers.

Table I

SUMMARY OF REPORTED CASES

	Sex	Age (yr.)	Bone Age	Lesions in Other Members of Family
Kirner,[4] 1927	F	13	—	—
Thomas,[8] 1936	F	8	—	—
	F	11	—	No
	F	12	—	—
Wilson,[9] 1952	M	11	11	No
	F	11	Bone age 14 when chronologic age 14	Clubbing of toes, not fingers, in mother and father
	F	5	—	Brother, father and paternal grandmother
	F	18	—	No
Brailsford,[1] 1953	M	10	—	—
	F	9	—	—
	M Both 5th and index fingers clubbed	13	—	—
	F	15	—	Mother and maternal aunt
Hippe,[2] 1953	F Two years later terminal phalanx curved but with normal trabeculation	12	—	—
Schmid,[6] 1957	F Twelve years later terminal phalanx curved but with normal trabeculation	9	—	—
Mercer,[5] 1959	F	11	11	—
Kaufmann and Taillard,[3] 1961	F	9	9	No
	M	10	10	—
Taybi,[7] 1963	M Only Negro observed with deformity	11	—	—

Table I (*Continued*)

	Sex	Age (yr.)	Bone Age	Lesions in Other Members of Family
Present Series	M	8		Sibling
	M	16	Retarded early	Sibling
	M	54		Uncle
	M	56		Father
	F	14	Retarded early	Index Case
	F	19		Sibling
	F	83		Paternal grandmother

fingers were curved and short.

Brailsford[1] considered the bowing to be familial; he saw it in the mother and aunt of an affected girl 15 years of age. Wilson[9] found it in the brother, father, and paternal grandmother of an affected girl 5 years of age.

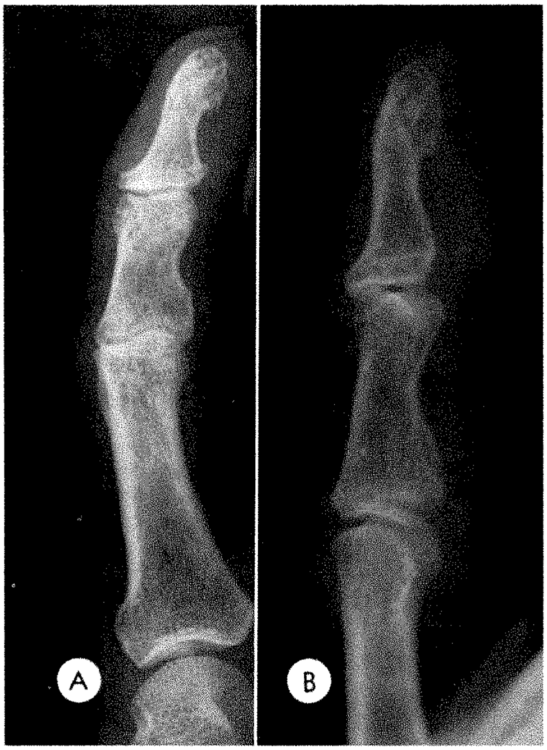

Fig. 9. (*A* and *B*) In the hands of the 54 year old uncle (Case 6) the bony deformity is present but it is not as marked as the soft tissue deformity.

The fingers of our first patient were normal when she was 18 months of age. The fingers of the 16 year old boy (Case 3) when he was $5\frac{1}{2}$ years of age did not show the deformity. Bone age was at that time retarded. It is likely that the lesion develops after birth, perhaps after the fifth year of life. In the 8 year old boy (Case 4), bone age is normal although the globular swelling of the tips of both fifth fingers is present.

In the 14 year old girl (Case 1) and the 16 year old boy (Case 3), the bony lesion is active. The fingers of the 19 year old girl (Case 2) and 2 of the 3 adults (Cases 5 and 6) have undergone bony restitution.

The lesion is apparently familial with transmission as a simple autosomal dominant.

SUMMARY

Isolated symmetric bowing of the shafts of the terminal phalanges of both fifth fingers, Kirner's deformity, is described in 7 members in 3 generations of 1 family. Transmission appears to be as an autosomal dominant. Roentgenograms show the deformity at various stages. Bone age may be retarded early before deformity of the fifth fingers appears and soft tissue

swelling precedes bowing bone deformities. Angulation takes place at the metaphysis, and the shaft is bent. Fusion of the ossification centers of the epiphysis and shaft follows, but the terminal phalanx remains bowed.

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STANDARDIZATION OF TERMINOLOGY AND EVALUATION OF OSSEOUS RELATIONSHIPS IN CONGENITALLY ABNORMAL FEET*

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THE terminology used in the radiologic and orthopedic literature to describe congenital deformities of the feet is confusing. Many different words have been employed by various authors[4,6,9,10,11,12] to describe the same condition. The problem is compounded, because the term "clubfoot" is applied to at least 8 different types of deformity.[6] The characteristic roentgenographic changes of congenital abnormalities of the feet are demonstrated briefly in one orthopedic[4] and one radiologic[10] text. A review of the radiologic literature revealed only 1 paper on this subject.[2] Various angles have been described to help determine foot abnormalities, but the normal range of these angles and their diagnostic significance are not well defined. A reproducible roentgenographic technique for obtaining weight-bearing studies of the feet is not strongly advocated or followed. The object of this communication is to standardize the terms and techniques used to describe and evaluate the deformities frequently encountered in congenitally abnormal feet. The normal range of angles formed by different bones of the feet as seen on weight-bearing anteroposterior and lateral roentgenograms are determined and their diagnostic significance is discussed.

TERMINOLOGY

Valgus, varus, equinus, calcaneus deformity, abduction and adduction are the 6 terms which will be used in this paper to describe positional deformities of the feet. The first 4 terms when used alone apply only to the feet.[1] Valgus means bent or turned away from the midline of the body. Varus means bent or turned towards the midline of the body. Either term may be applied to the forefoot, hindfoot, or entire foot. Equinus refers to an abnormal elevation of the posterior part of the calcaneus. Calcaneus deformity applies to an increased vertical position of the calcaneus with depression of the posterior part of the calcaneus. Abduction means to draw the foot away from the sagittal axis of the body, and adduction means to draw the foot towards the sagittal axis of the body. There is no element of rotation in these last 2 definitions.

Because there are so many types of "clubfoot," this term has become meaningless. The word "talipes," which means ankle (talus) and foot (pes), does not increase the understanding of a deformity and will not be used. Pronation and supination properly refer to positions of the hand.[4] Inversion, eversion, dorsiflexion and plantarflexion are general descriptive terms applied to many parts of the body.

ROENTGENOLOGIC TECHNIQUE

Standardization of a technique for roentgenographic examination of the feet is very important. Only weight-bearing views are reliable for comparison studies and for demonstrating abnormalities adequately. The anteroposterior projection of the feet in infants and young children is taken with the patient in the sitting or supine position. The knees are held together without internal or external rotation of the lower extremities. If there is marked forefoot varus or adduction, the knees are separated slightly to avoid overlap of the two feet. The legs must be parallel to each other and perpendicular to the cassette in the medial-lateral plane (Fig. 1*A*). The forefoot is held firmly to the cassette by means of a thin plastic board pressed on the dorsal aspect of the foot.

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For the lateral view in infants and young children, the leg is stabilized by being held firmly with one hand. A plastic board is pushed against the sole of the foot with the other hand (Fig. 1*B*). It is important that the leg be perpendicular to the plastic board in both the anteroposterior and medial-lateral plane. Roentgenograms in each lateral view are taken separately. Simultaneous lateral roentgenograms of the feet with the lower extremities in a frog-leg position produce unavoidable distortion.

In older children, standing anteroposterior and lateral roentgenograms of the feet are taken. The examination is completed by taking nonweight-bearing oblique roentgenograms.

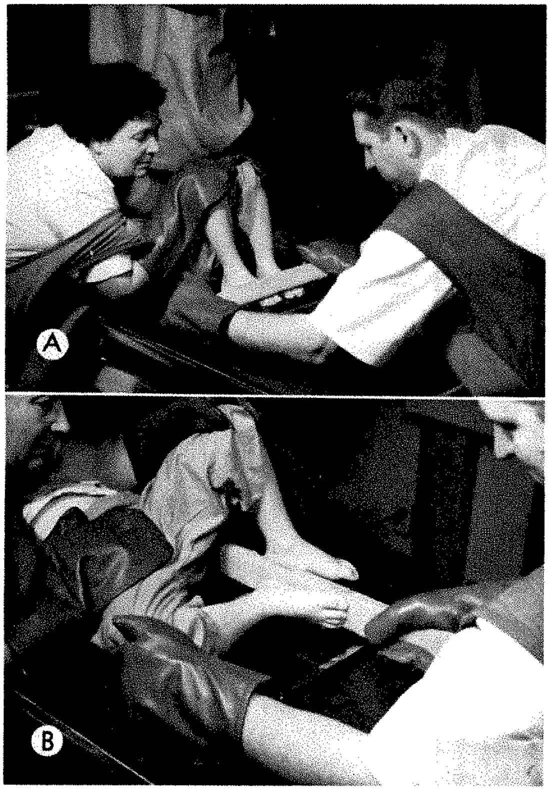


Fig. 1. Techniques for taking weight-bearing roentgenograms in a young child. (*A*) In the anteroposterior projection the legs are parallel to each other and perpendicular to the cassette in the medial-lateral plane. (*B*) In the lateral projection the leg is stabilized by the left hand and a plastic board is pushed against the foot with the right hand. An overhead tube position is utilized in taking roentgenograms in both views.

NORMAL FINDINGS

One hundred and sixty weight-bearing anteroposterior and lateral roentgenograms of the feet were obtained in normal children from ages 12 days to 12 years. The normal range of the commonly employed talo-calcaneal, calcaneal-fifth metatarsal, and mid talar-mid calcaneal angles were determined.

The normal talo-calcaneal angle is shown in Figure 2*A*. This is a line drawing of a normal 4 year old weight-bearing foot in the anteroposterior projection. At this age and in older children, a line drawn through the long central axis of the talus usually passes just medial to the base of the first metatarsal. A line through the long mid axis of the calcaneus tends to pass through the medial aspect of the base of the fourth metatarsal. In infants and young children the long central axis of the talus is shifted medially. The talo-calcaneal angle varied in normal children from 15 to 50 degrees and was age dependent (Fig. 3). In infants and young children the talo-calcaneal angle was between 30 and 50 degrees. There was a progressive decrease in this angle up to the age of 5 where the lines of the graph are seen to level off. In children older than 5 years the talo-calcaneal angle varied from 15 to 30 degrees.

Figure 4*A* is a line drawing of a normal weight-bearing foot in the lateral projection. A line drawn through the long axis of the calcaneus forms an acute angle with a line through the mid axis of the talus. This mid talar-mid calcaneal angle was found to vary normally from 25 to 50 degrees. A line drawn through the inferior cortex of the body of the calcaneus makes an obtuse angle with a line through the inferior cortex of the fifth metatarsal. The normal range for this calcaneal-fifth metatarsal angle was 150 degrees to 175 degrees. The normal range of these angles as seen in the

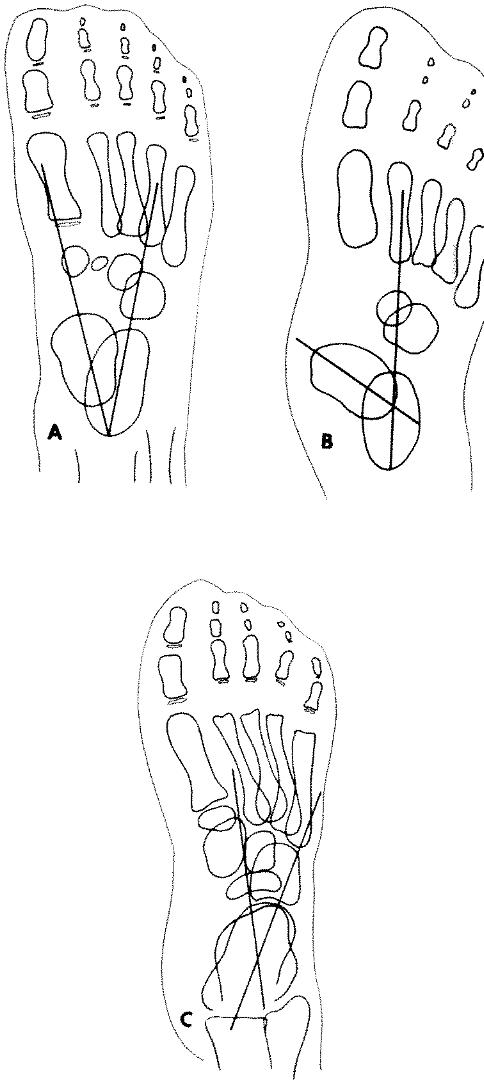


Fig. 2. Anteroposterior line drawings of weight-bearing feet. (*A*) Normal 4 year old in whom the talo-calcaneal angle measures 25 degrees. At this age the mid talar line passes through the medial cortex of the first metatarsal and the mid calcaneal line passes through the medial portion of the fourth metatarsal. (*B*) This 2 year old has severe hindfoot valgus. The talo-calcaneal angle is 58 degrees. (*C*) Hindfoot varus is demonstrated in an 8 year old. Even though the relationship of the talus and calcaneus is markedly altered, the talo-calcaneal angle measures 29 degrees. There is some varus deformity of the forefoot.

lateral view did not vary with the age of the child as did the talo-calcaneal angle.

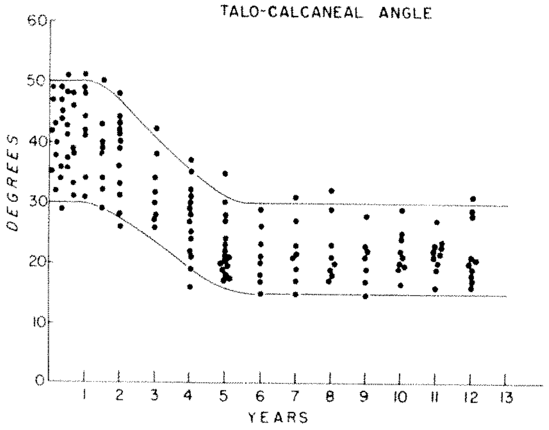


Fig. 3. One hundred and sixty weight-bearing anteroposterior roentgenograms of the feet were obtained in normal children from ages 12 days to 12 years. The normal variation of the talo-calcaneal angle is seen to be age dependent, up to the age of 5 years.

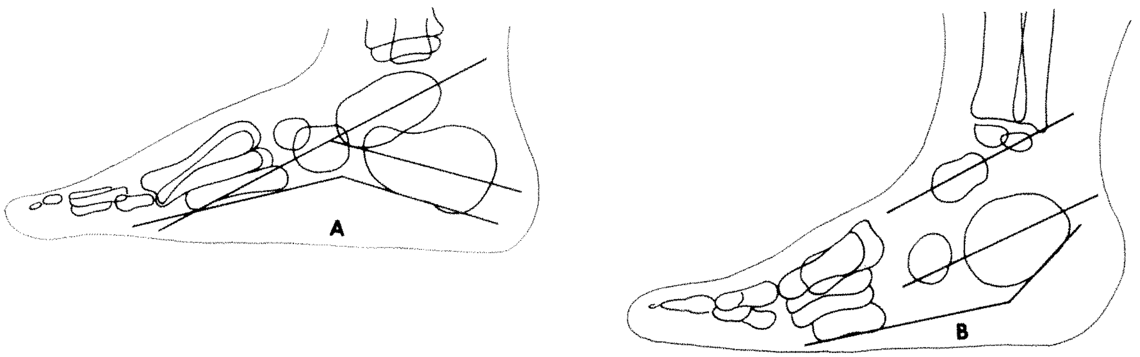
It is generally thought that a line drawn through the central long axis of the talus passes longitudinally through the shaft of the first metatarsal on a lateral weight-bearing roentgenogram. This usually is true in children over 5 years of age, but in infants and young children the talus is positioned more vertically and the mid talar line passes inferior to the shaft of the first metatarsal (Fig. 9 *B*).

CONGENITAL ABNORMALITIES

The changes in hindfoot valgus are shown by a line drawing in Figure 2*B*. The distal part of the calcaneus rotates laterally from under the talus. The cuboid, cuneiforms, metatarsals, and navicular undergo a variable amount of abduction. The long axis of the talus is directed medial to the first metatarsal, and the talo-calcaneal angle usually is increased depending on the patient's age.

Varus of the hindfoot is shown in Figure 2*C*. The distal part of the calcaneus rotates medially under the talus. The talo-calcaneal angle may be less than 15 degrees, but even in severe deformities the talo-calcaneal angle may be within normal limits (Fig. 2*C* and 5*A*).

Equinus position of the hindfoot with elevation of the posterior part of the calcaneus is shown in Figure 4*B*. The mid



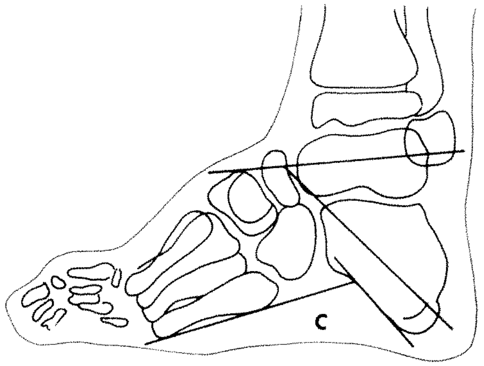


Fig. 4. Lateral line drawings of weight-bearing feet. (*A*) A normal 4 year old in whom the acute mid talar-mid calcaneal angle measures 42 degrees. The obtuse calcaneal-fifth metatarsal angle is 152 degrees. (*B*) There is equinus with elevation of the posterior part of the calcaneus in this 15 month old child. The angles are grossly altered. (*C*) This 12 year old has calcaneus deformity. The posterior part of the calcaneus is depressed, and there is a characteristic "box-like" appearance of the calcaneus. The mid talar-mid calcaneal angle measures 48 degrees and the calcaneal-fifth metatarsal angle is 115 degrees.

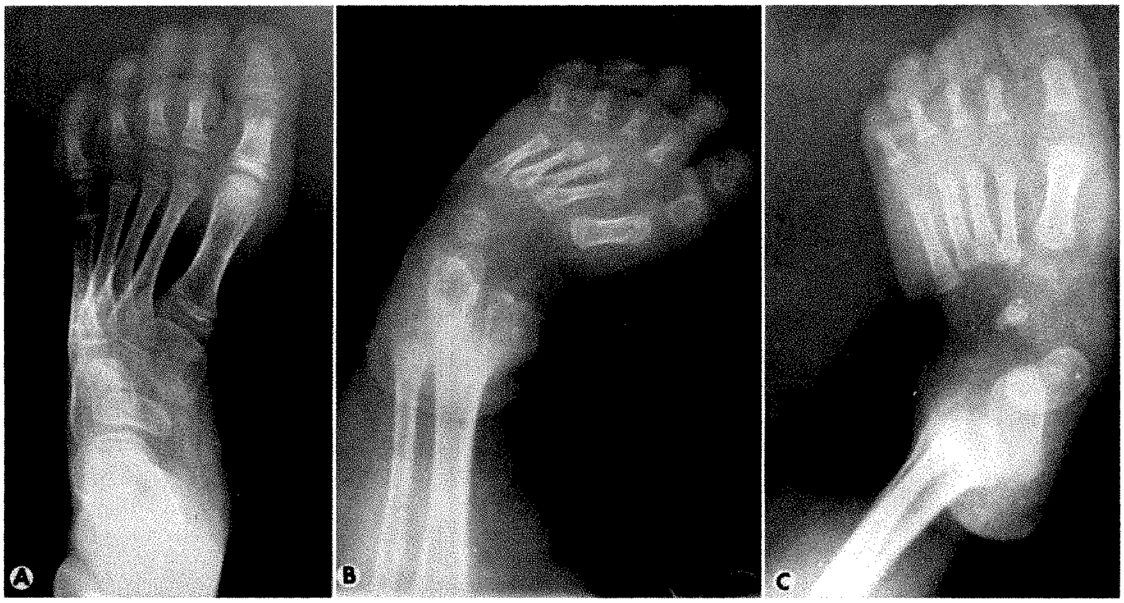


Fig. 5. (*A*) Severe varus deformity of the entire foot with slight forefoot adduction. The talo-calcaneal angle is within normal limits and measures 25 degrees. (*B*) There is marked forefoot adduction. The superimposition of the talus and calcaneus indicates hindfoot varus. The talo-calcaneal angle is about 19 degrees, which is too small for a 4 month old. (*C*) Severe hindfoot valgus is demonstrated in a 5 month old. The talo-calcaneal angle measures 61 degrees. There is forefoot abduction.

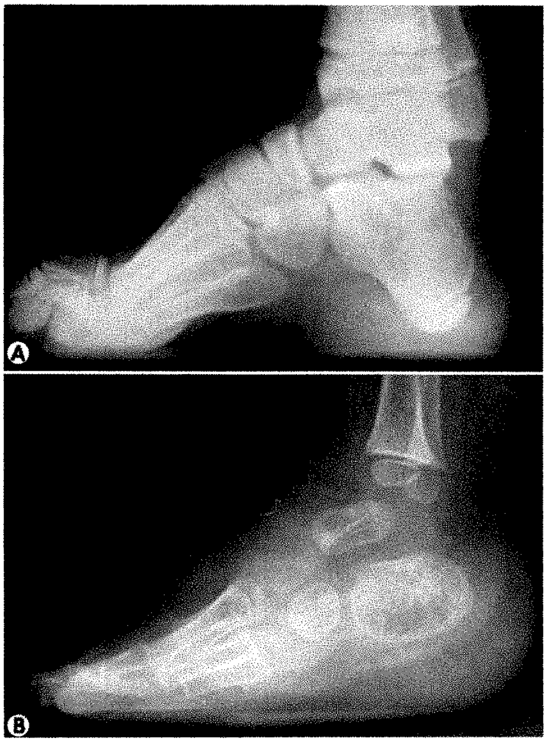


Fig. 6. (*A*) Calcaneus deformity is demonstrated in a 12 year old. The calcaneus appears short and "box-like." The talus is horizontal. The mid talar-mid calcaneal angle is at the upper limits of normal (48 degrees) and the calcaneal-fifth metatarsal angle is decreased (115 degrees). (*B*) Equinus deformity with elevation of the posterior part of the calcaneus is demonstrated in this 15 month old. All the angles are altered.

talar line frequently is more horizontal than normal, and the mid calcaneal line rotates from its normal direction. It may never form an angle with the mid talar line. The obtuse angle formed between the inferior calcaneus and the fifth metatarsal is increased beyond 175 degrees.

Calcaneus deformity is illustrated in Figure 4*C*. The mid-talar line is more horizontal than normal but still may form a normal angle with the more vertical mid calcaneal line. In severe calcaneus deformity, this angle is increased beyond 50 degrees. The obtuse angle formed by lines drawn through the inferior cortex of the body of the calcaneus and the fifth metatarsal usually is less than 150 degrees. In addition to the abnormally vertical position of the calcaneus, there is an apparent shortening of the neck of this bone which produces a characteristic "box-like" appearance.

DISCUSSION

The firm anatomic relationship of the talus to the tibia in the ankle joint mortice prevents any significant medial or lateral motion of the talus. Therefore, hindfoot valgus or varus occurs at the sub-talar and talo-navicular joints and to a slight degree at the calcaneal-cuboid joint. A diagnosis of hindfoot varus or valgus requires a malalignment of the calcaneus relative to the talus as demonstrated on anteroposterior weight-bearing roentgenograms.

Figure 5*A* is a roentgenogram showing varus of the entire foot. The talus and calcaneus are superimposed on each other because the calcaneus has rotated medially under the talus. In spite of these gross abnormalities, the talo-calcaneal angle measures 28 degrees, which is within normal limits. The second, third, fourth, and fifth metatarsals are superimposed abnormally. There is slight adduction of the forefoot. Figure 5*B* demonstrates marked adduction of the forefoot. There is very little superimposition of any of the metatarsals. There is, however, marked varus of the heel as indicated by the superimposition of the talus and calcaneus. Marked valgus of the hindfoot is demonstrated in Figure 5*C*. The calcaneus has rotated from under the talus in a lateral direction. The talo-calcaneal angle is increased markedly. There is slight abduction of the forefoot.

Figure 6*A* demonstrates a severe calcaneus deformity. The calcaneus shows the characteristic "box-like" deformity. The mid talar-mid calcaneal angle is at the very upper limits of normal. The talus is more horizontal than normal. Equinus deformity is demonstrated in Figure 6*B*. The inability of the patient to place his heel flatly on the ground is evidenced by the cephalad angulation of the posterior aspect of the calcaneus. The talus is more horizontal than normal and the angle between the mid talar and mid calcaneal axes is nearly zero.

A discussion of the different types of congenital flatfoot is beyond the scope of this paper. However, the common mobile congenital flatfoot is demonstrated in Figure 7, *A* and *B*. There is marked valgus of the hindfoot with the talus pointing in a medial direction (Fig. 7*A*). It is interesting to note that the talo-calcaneal angle in this patient is well within normal limits. There is some abduction of the forefoot. In the lateral view (Fig. 7*B*), the longitudinal arch is flat. The calcaneus is more horizontal than normal but not in an equinus position. The talus is rotated vertically, but the angle between the mid talar and the mid calcaneal lines may be within the upper limits of normal.

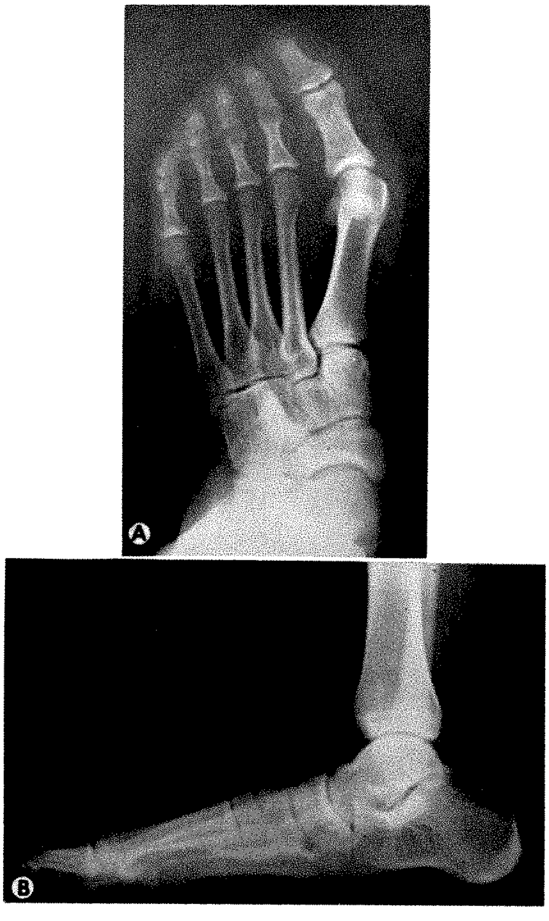


FIG. 7. This 12 year old demonstrates the mobile type of flatfoot. (*A*) The talo-calcaneal angle is 29 degrees which is within normal limits, yet there is valgus of the hindfoot with marked medial deviation of the talus. (*B*) The lateral view demonstrates a flat longitudinal arch. There is no equinus deformity and the mid talar-mid calcaneal angle is within normal limits (46 degrees).

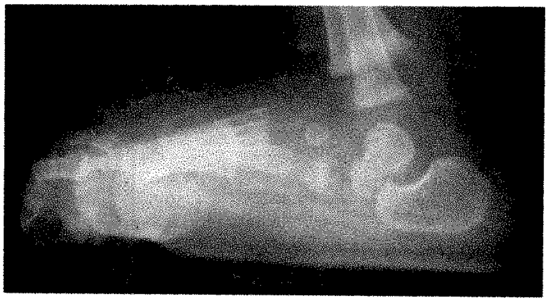


FIG. 8. This 5 month old has the "vertical talus" type of flatfoot. The talar head is dislocated from the navicular and there is a mild equinus deformity.

The roentgenographic changes found in congenital flexible flatfoot (Fig. 7, *A* and *B*) should be differentiated from the changes characteristic of a distinct entity called "vertical talus."[5,7] This congenital abnormality presents clinically as a rigid type of flatfoot, and there is a prominent soft tissue mass along the mid-sole of the foot produced by the talar head. Roentgenographically, the talus is nearly vertical, and there is a dislocation of the talar head from the navicular (Fig. 8). The tibia articulates with the very posterior part of the articular surface of the talus. The hindfoot is in equinovalgus, and the forefoot is abducted. The equinus deformity and the extreme vertical position of the talus differentiate this entity from the mobile type of congenital flatfoot.

Cavus or clawfoot is another distinct foot abnormality characterized by a high longitudinal arch and clawing of the toes. The calcaneus in a cavus foot is normal as opposed to the "box-like" appearance of the calcaneus in calcaneus deformity.

The diagnostic value of the different angles of the foot is open to question. The talo-calcaneal angle is wider in infants than in older children. The central axis of the talus is shifted somewhat medially in the anteroposterior weight-bearing view and

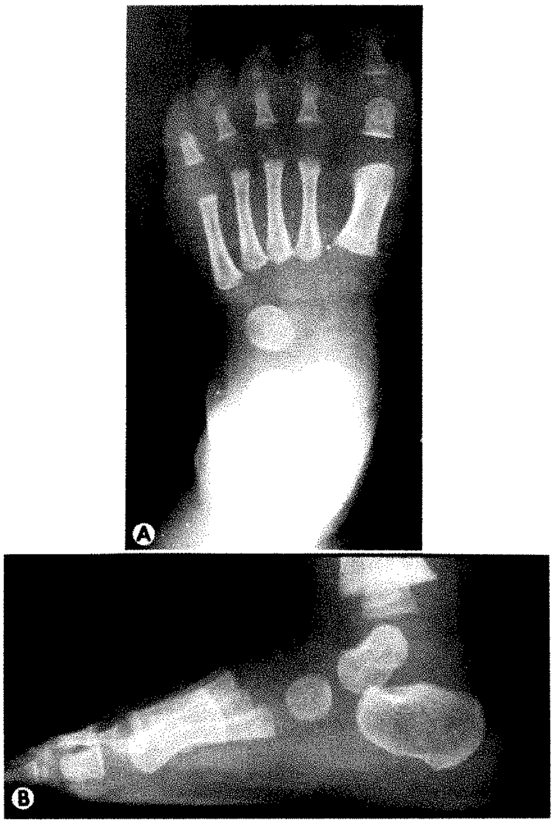


Fig. 9. Normal anteroposterior and lateral weight-bearing roentgenograms of a 13 month old. (*A*) The medial position of the mid talar axis and the wider talo-calcaneal angle (45 degrees) are well demonstrated. (*B*) The lateral view shows the more vertical position of the talus which is characteristic for this age.

somewhat vertically in the lateral view in infants and young children (Fig. 9, *A* and *B*). These changes reflect the laxity of the ligamentous structures. The angles identified in the lateral view give a range of normal values that are independent of the patient's age.

Figures 5*A* and 7*A* are examples of normal talo-calcaneal angles in older children who have marked varus and valgus deformities of the hindfoot, respectively. The talo-calcaneal, calcaneal-fifth metatarsal or mid talar-mid calcaneal angles may be used as preliminary guides in evaluating a weight-bearing roentgenogram, but a single normal or abnormal angle cannot be used as the basis for a diagnosis.

The diagnosis of congenital foot abnormalities is based primarily on physical examination of the patient. Roentgenographic evaluation is performed to exclude clinically unsuspected abnormalities and to assess and document the evolution of the deformity. The final roentgenographic interpretation is subjective and must depend on the relationship and position of individual bones and groups of bones to each other.

CONCLUSION

Valgus, varus, equinus, calcaneus deformity, abduction and adduction are the best terms to describe congenital abnormalities of the feet. The terms "talipes" and "clubfoot" do not contribute to understanding or evaluating a foot abnormality. Proper roentgenographic technique and interpretation require weight-bearing studies.

The normal range for the angles frequently used to evaluate the foot is presented. These angles may be utilized as a guide in determining foot abnormalities. However, the final diagnosis depends on physical examination of the patient and subjective roentgenologic evaluation of the interrelationship of the osseous structures.

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EARLY DIAGNOSTIC AND PROGNOSTIC SIGNS IN LEGG-CALVÉ-PERTHES DISEASE[*]

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THE typical changes that occur in the femoral epiphysis with Legg-Calvé-Perthes disease have been described repeatedly in the literature.[2,7,10] The importance of early diagnosis is stressed as a guide to institution and evaluation of treatment.[1,4,6] It has also been recognized that one of the earliest signs is a widening of the distance, as seen on the anteroposterior roentgenogram, from the lateral margin of the so-called pelvic teardrop[5] to the medial border of the proximal femoral metaphysis[9,13,14] (Fig. 1). To our knowledge, no one has reported measurements of this distance—which will be referred to in this paper as the teardrop distance (TDD)—either in normal or in abnormal hips.

Another roentgenographic finding is the presence of lucent lesions in the proximal metaphyses of involved femurs. Certain authors believe that the extent of this metaphysial involvement is important to prognosis,[1,8] while others do not.[2,3]

For these reasons, we decided (1) to measure the TDD in normal and diseased hips and to evaluate these measurements as a basis for diagnosis, and (2) to assess the prognostic value of early changes in the femoral metaphysis.

MATERIALS AND METHODS

TDD MEASUREMENTS

For purposes of comparison, the TDD was measured on roentgenograms of 1,070 normal hips. Measurements were made on anteroposterior roentgenograms of the pelvis and hips. Positioning of the patient for the roentgenogram did not alter the measurement, provided the femur was not rotated internally or externally more than 30 degrees, flexed more than 30 degrees, or abducted more than 15 degrees. Measurements were reproducible within 1 mm.

Data were compiled on 53 patients with unilateral and 8 with bilateral Legg-Calvé-Perthes disease. All were seen at the Children's Hospital of the East Bay, Oakland, California, from 1949 to 1963. The age range was 1–12 years. There were 51 males and 10 females. Five males and 3 females had bilateral involvement.

The TDD was measured on roentgenograms of 49 hips with early involvement and 38 of the normal contralateral hips (Fig. 1, 4, 6, 8 and 10). In certain cases, additional measurements were made during the course of the disease.

ASSESSMENT OF METAPHYSIAL LESIONS

All grading of metaphysial lesions was done on the frog leg lateral roentgenogram, which presents the epiphysis as a line, in contrast to the plane often presented on the anteroposterior roentgenogram. Only by the use of lateral views can metaphysial lesions be differentiated from epiphysial lesions in every case.

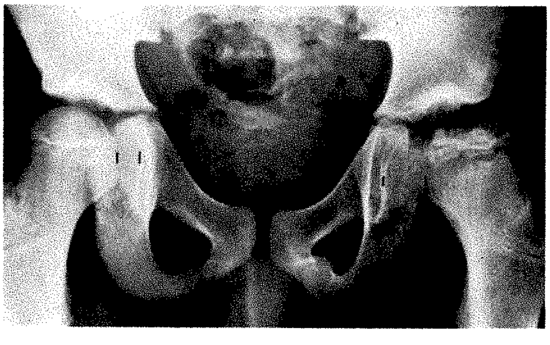

FIG. 1. Anteroposterior roentgenogram of hips of A. T., a 9 year old white boy, 6 months after onset of the limp on the left side (5/18/50). The TDD (teardrop distance) is indicated by the vertical lines: right, 8 mm., left, 16 mm.

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The lesions have been graded as follows: minimal—one or more lesions less than 5 mm. in diameter not isolated from the epiphysial line (Fig. 2); intermediate—one or more lesions 5–10 mm. in diameter adjoining the epiphysis, or several lesions 3–5 mm. in diameter isolated from the epiphysial line (Fig. 5); extensive—one or more lesions 10 mm. or greater adjoining the epiphysis or several lesions 5–10 mm. isolated from the epiphysial line (Fig. 7 and 9).

Metaphysial lesions appeared to enlarge early, then to decrease in size as the femoral head flattened and reorganization proceeded. The greatest extent of metaphysial involvement seen on any lateral roentgenogram of the hip during the course of the disease was used as a basis for prognosis. Grading of the lesions was done without knowledge of the outcome of the case.

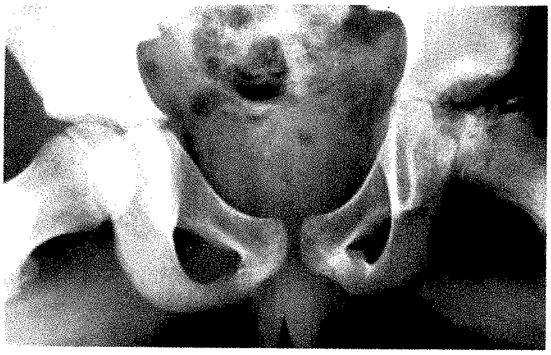

Fig. 2. Lateral roentgenogram of hips of A. T., showing minimal metaphysial involvement of left femur (5/18/50).

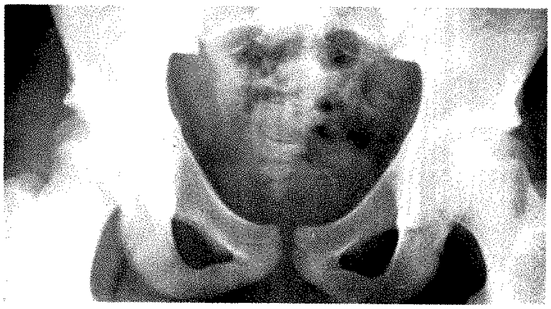

Fig. 3. Left hip of A. T. was virtually normal roentgenographically on 1/20/54. TDD: right, 8 mm., left, 11 mm. The clinical outcome in this case was good.

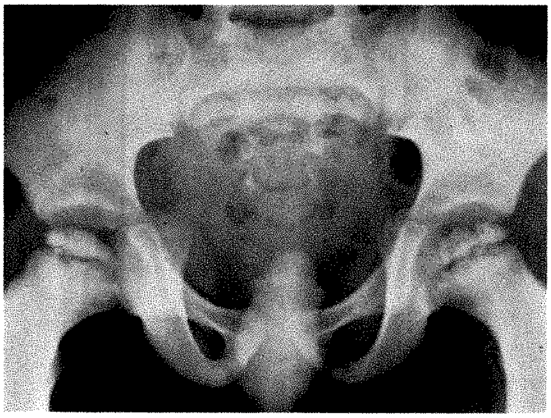

Fig. 4. Anteroposterior roentgenogram of hips of R. E., a 4 year old white boy, 3 months after onset of pain in the left hip. TDD: right, 11 mm., left, 10 mm.

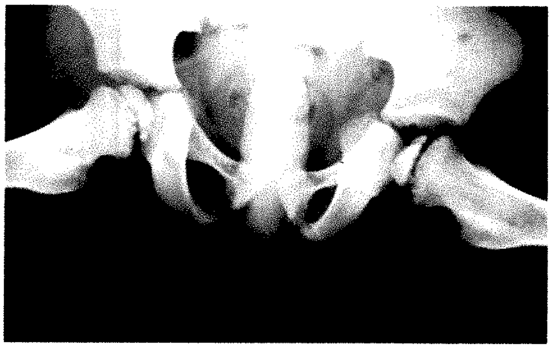

Fig. 5. Lateral roentgenogram of hips of R. E., showing intermediate metaphysial involvement bilaterally (4/23/52). The clinical outcome was good for both hips (10/18/62).

Adequate information for comparison of extent of lesions and outcome was obtained with regard to 43 hips (26 which were observed for less than 2 years were excluded from analysis of end results). The outcome was classified as bad if one or more of the following conditions existed after 2 years: (1) pain at rest or with normal exercise, (2) limitation of motion greater than 40 per cent of the full range of normal,* (3) leg shortening of more than $\frac{3}{4}$ inch. These criteria were selected because we believe function of the hip to be the most important consideration in determining the outcome of this disease. Furthermore, it has

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* The total normal range of flexion, rotation, abduction, and adduction has been taken as 300 degrees.[12]

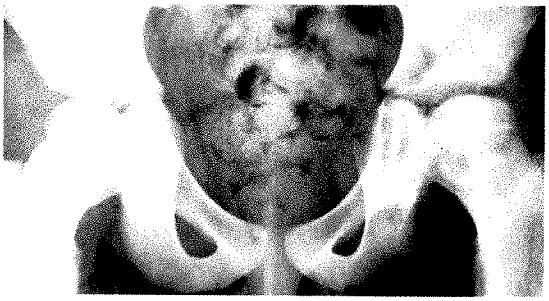

Fig. 6. Anteroposterior roentgenogram of hips of B. B., a 10 year old white boy, 6 months after onset of pain in the left hip (8/30/51). TDD: right, 9 mm., left, 12 mm.

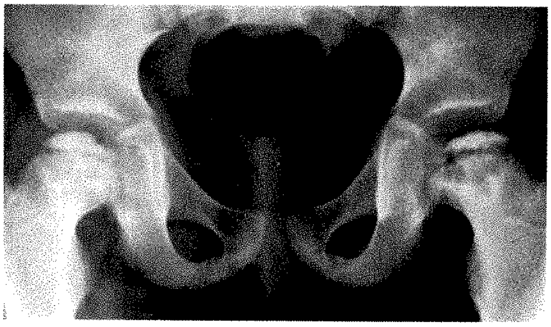

Fig. 8. Anteroposterior roentgenogram of hips of D. T., a 4 year old white girl, 12 months after onset of pain and limp mostly on the right side (1/22/54). TDD: right, 12 mm., left, 11 mm.

been shown that functional result is closely related to roentgenographic appearance.[3] The outcome was classified as good if none of these conditions was present after a period of 2 years.

RESULTS

TDD MEASUREMENTS

The TDD measurements of 1,070 normal hips of persons 6 months to 11 years of age are given in Figure 11. The TDD of normal hips ranged from 5–12 mm., with a mean value of 8.8 mm. Ninety-five per cent (2 standard deviations) of all measurements were between 6 and 11 mm. There was no relation between the TDD and the age of the patient.

TDD measurements of 49 hips affected by Legg-Calvé-Perthes disease and of 38 contralateral hips are given in Figure 12.

In Figure 13 is shown the difference between the TDD measurements of the two hips in 535 normal persons, and this difference in 39 persons with unilateral Legg-Calvé-Perthes disease. In the first group, the difference was 1 mm. or less in 96 per cent of the cases. In the persons with Legg-Calvé-Perthes disease, however, it was 1 mm. or less in only 30 per cent.

It was occasionally possible to observe an increase in the TDD in the absence of other roentgenographic changes in the early stage of the disease. This finding was of particular value in bilateral cases in which one side became involved later than the other; it was noted in 3 of 8 of these persons.

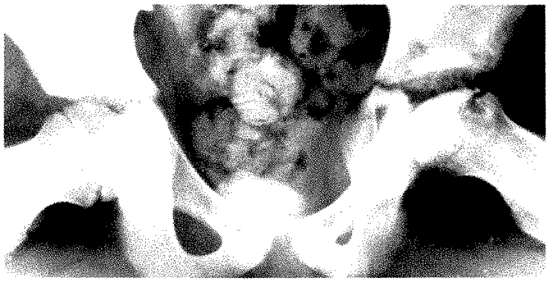

Fig. 7. Lateral roentgenogram of hips of B. B., showing extensive metaphysial involvement (8/30/51). The final outcome (2/20/63) was bad because of shortening of $1\frac{1}{2}$ inches.

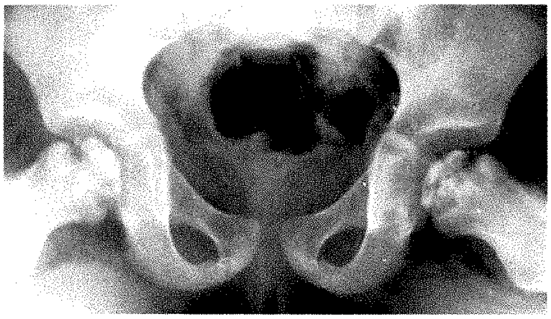

Fig. 9. Lateral roentgenogram of hips of D. T., showing extensive metaphysial involvement bilaterally. The final outcome for both hips was bad because of limitation of motion (2/22/63).

ASSESSMENT OF METAPHYSIAL LESIONS

Correlation of the extent of the metaphysial lesion with final outcome is presented graphically in Figure 14.

The final outcome was good, as defined

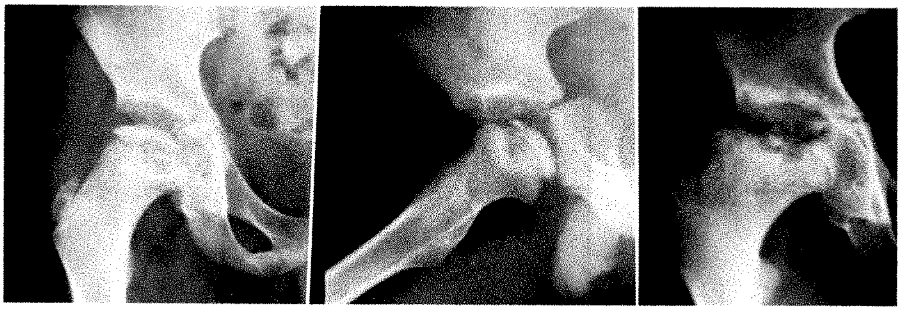

Fig. 10. Roentgenograms of right hip of J. S., a 9 year old white boy, 14 months after onset of pain and limitation of motion in right hip. Roentgenograms 5 months previously were interpreted as normal, but TDD was 11 mm. *Left.* Anteroposterior view (6/10/59); TDD is 14 mm. *Center.* Lateral view (6/10/59), showing extensive metaphysial involvement. *Right.* Anteroposterior view (3/15/63), showing widening and shortening of the neck of the femur. The outcome was classified as bad because of limitation of motion.

above, in 63 per cent of the cases. However, when the patients were grouped according to extent of metaphysial involvement, the outcome was good in 91 per cent of the group with minimal metaphysial lesions, in 63 per cent of the group with intermediate lesions, and in 8 per cent of the group with extensive lesions.

In this series, the principal mode of therapy was selected without regard to sex, age, or the extent of metaphysial disease. Therapy consisted of spica casts, patten-bottom braces, and bed rest, in approximately equal numbers of cases. Five patients received no treatment.

There was no correlation between final outcome and age, sex, or mode of therapy. However, if a good outcome was predicted for all hips with minimal metaphysial lesions and a bad outcome for those with extensive lesions, an accuracy of 91 per cent resulted (Fig. 1, 2, 3, 6, 7, 8, 9 and 10). Of 8 hips with intermediate lesions (Fig. 4 and 5), the outcome was good in 5 cases and bad in 3.

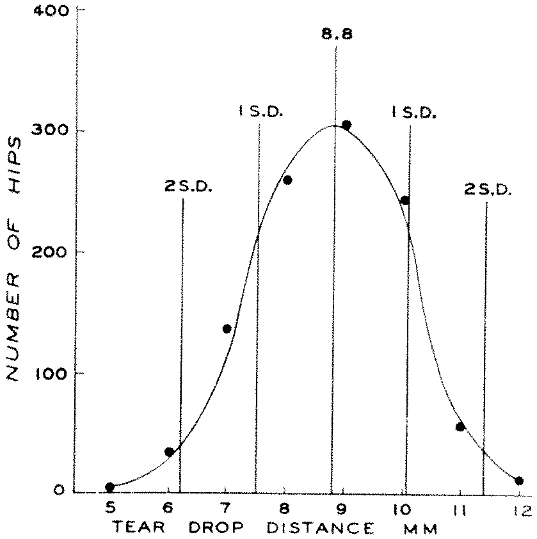

Fig. 11. Measurements of TDD in 1,070 hips (535 persons, 6 months to 11 years of age) with no known hip joint disease. Mean measurement is 8.8 mm., with a standard deviation of 1.3 mm. Ninety-five per cent of all measurements are between 6 and 11 mm.

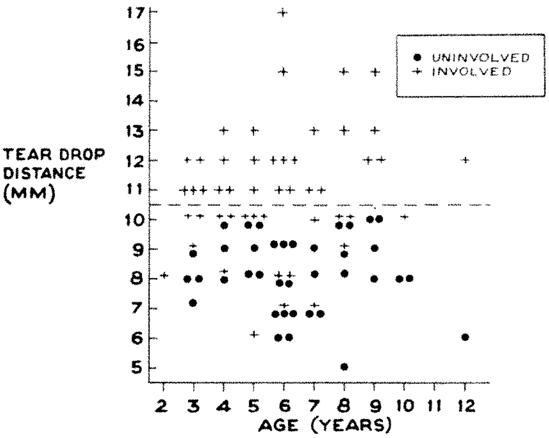

Fig. 12. Comparison of TDD of 49 hips affected by Legg-Calvé-Perthes disease and 38 contralateral hips. No normal hip had a TDD greater than 10 mm. or greater than the TDD of the affected hip. If the difference was at least 2 mm., the disease was invariably present in the hip with the greater TDD.

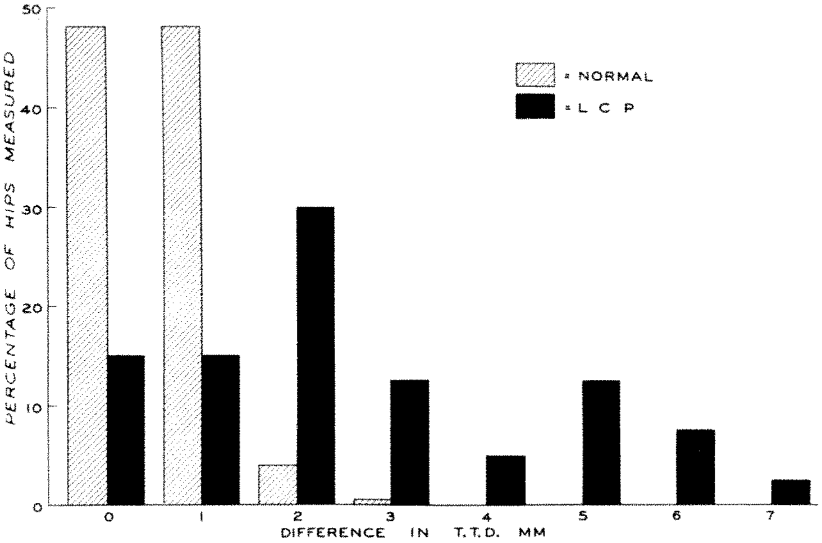

Fig. 13. Difference between TDD measurements of hips of 535 persons with no known hip joint disease and 39 with unilateral Legg-Calvé-Perthes disease, expressed as percentage of total number of hips measured.

DISCUSSION

TDD MEASUREMENTS

Measurement of the TDD in 1,070 persons with no known hip joint disease indicates that this distance is constant within a narrow range and is affected only minimally by variations in positioning of the subject. The measurements were reproducible within 1 mm. and were found to be independent of the age of the subject.

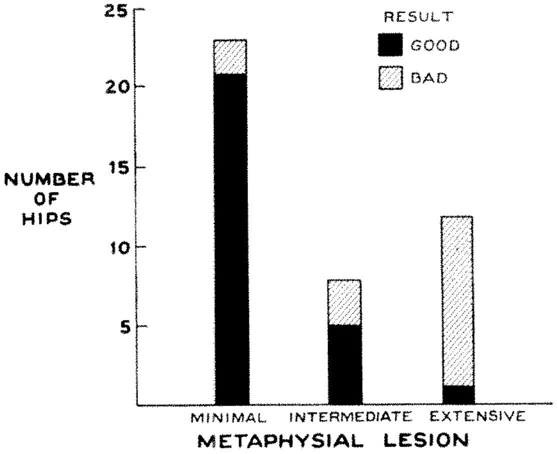

Fig. 14. Comparison of extent of metaphysial involvement with outcome as evaluated 2 to 14 years after diagnosis of Legg-Calvé-Perthes disease. Of hips with minimal involvement, outcome was good in 91 per cent. Of hips with extensive involvement, outcome was good in only 8 per cent.

Diagnosis of Legg-Calvé-Perthes disease has often been delayed because of absence of positive findings on roentgenograms of the hip at the time of onset of symptoms. Increase in the TDD to more than 11 mm. has proved to be an indication of hip joint disease. Also, a difference of 2 mm. or more between the TDD's of both hips is highly suggestive of a pathologic condition in the hip with the larger TDD. It should be emphasized that these changes are not specific for Legg-Calvé-Perthes disease but are confirmatory in those cases in which clinical evaluation and laboratory tests suggest this diagnosis.[9]

ASSESSMENT OF METAPHYSIAL LESIONS

It is well known that the extent of involvement, as indicated by a variety of factors, differs greatly from case to case and is closely related to the outcome of the disease.[1,2,4,7,8,11,13] Our findings show that the extent of involvement of the metaphysis indicates the extent of disease and is therefore an accurate guide to prediction of outcome (Fig. 1 through 10, inclusive).

We have been able to correlate outcome

with minimal or extensive involvement in 91 per cent of cases independently of age, sex, or mode of therapy, as long as 6 years before the head of the femur was completely healed.

SUMMARY

The teardrop distance (TDD), the distance from the lateral margin of the pelvic teardrop to the medial border of the proximal femoral metaphysis, has been measured in 49 hips affected by Legg-Calvé-Perthes disease. TDD measurements of 1,070 normal hips of persons from 1–11 years of age have also been made. The TDD, when greater than 11 mm. or more than 2 mm. greater than that of the opposite hip, was found to be a sensitive indicator of hip joint disease.

The size and location of metaphysial lesions have been correlated with the final outcome. The accuracy of prediction of outcome, based on this correlation, was 91 per cent.

The extent of metaphysial involvement, measured on a lateral roentgenogram of the hip in the early course of Legg-Calvé-Perthes disease, was more useful in predicting the outcome than was age at onset or mode of therapy, both of which were found to be unrelated to outcome.

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GROWTH AND DEVELOPMENT OF THE VERTEBRAL BODY IN THE PRESENCE AND ABSENCE OF NORMAL STRESS*

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ONE of the important sequelae of man's assumption of the erect posture for ambulation has been the production of vertebral column stresses which differ from those of the quadruped. These stresses have phylogenetically resulted in a shortening of the vertebral column; a relative decrease in the height of the individual vertebra and an absolute decrease in the number of vertebral bodies have occurred.[11]

For a variety of reasons, some children never develop the capacity to stand erect and, hence, their vertebrae are not subject to normal stresses. This escape from the normal weight bearing condition results in increased vertical growth of the vertebral bodies.

The American orthopedic literature is replete with references to Heuter[19] and Volkmann[35] who recognized that stress or pressure applied parallel to the axis of growth inhibits the rate of growth and, conversely, that decreased pressure favors growth.[2,5] Delpech,[13] in 1829, however, was probably the first to recognize this relationship which has great applicability in the study of spinal growth.

The purpose of the authors is to briefly review the normal growth and development of the human vertebra and to demonstrate that in the absence of the usual gravitational pressures and biologic stresses, longitudinal overgrowth of the vertebrae occurs.

ORIGIN, GROWTH, AND DEVELOPMENT OF THE NORMAL VERTEBRAL BODY

The axial skeleton differentiates from mesenchyme, most of which originates in serially arranged pairs of mesodermal somites. During the fourth week of intrauterine life, an aggregate of mesenchyme from each somite, designated a sclerotome, migrates toward the notochord. This sclerotomic mesenchyme then forms paired segmental masses which are separated cephalad and caudad by intersegmental arteries. The caudal one-half proliferates faster and is separated from the cephalad half by a fissure. The component parts of the adjacent sclerotomes then reunite by the denser caudal part of each original sclerotome joining the looser cranial half of the sclerotome next caudad. These recombinations, not the primitive sclerotomes, are the primordia of the definitive vertebrae. Since a vertebra develops from two adjacent sclerotomes, the originally intersegmental arteries now pass midway over the vertebral body.[1]

Centers of chondrification begin to appear during the seventh intrauterine week and at 9 weeks vertebral ossification occurs. The primary ossification center for the vertebral body appears dorsal to the notochord, first in the lower thoracic region. The process spreads cephalad and caudad until by the twentieth week centers have appeared in all bodies except the two lowermost sacral vertebrae, where they may not appear until the thirtieth week, and in the coccyx where they may not appear until after birth.[21]

In the newborn child, the vertebral body ossification centers are ovoid as seen in the lateral roentgenogram[18,34] (Fig. 1). The height of the body at this time is about that of the adjacent disk space. The vertebral body exhibits anterior and posterior central indentations caused by the previously mentioned intersegmental arteries.

Gradually, between the ages of 2 and 5 years, the vertebral body becomes rectangular, its height being less than its anteroposterior dimension. There is also a decrease in the intervertebral disk space relative to the vertebral height.[23]

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Between 6 and 8 years of age, step-like recesses appear at the superior and inferior aspect of the vertebral margin (Fig. 2). These represent early cartilaginous precursors of an annular rim surrounding the margins of the vertebrae. Small calcific foci then appear in these cartilaginous rims. Gradually, these foci coalesce, ossify (Fig. 3) and, finally, fusion of the rim and vertebral body occurs.

The vertebral rim adds nothing to the longitudinal growth of the vertebra. Schmorl and Junghanns[33] have demonstrated that it is an error to compare the vertebral rim to the epiphysis of a long bone since there is no growth layer facing the disk and, hence, it is not in fact an epiphysis. Bick and Copel[8] term the vertebral rim "the ring apophysis," believing this will clarify its nature.

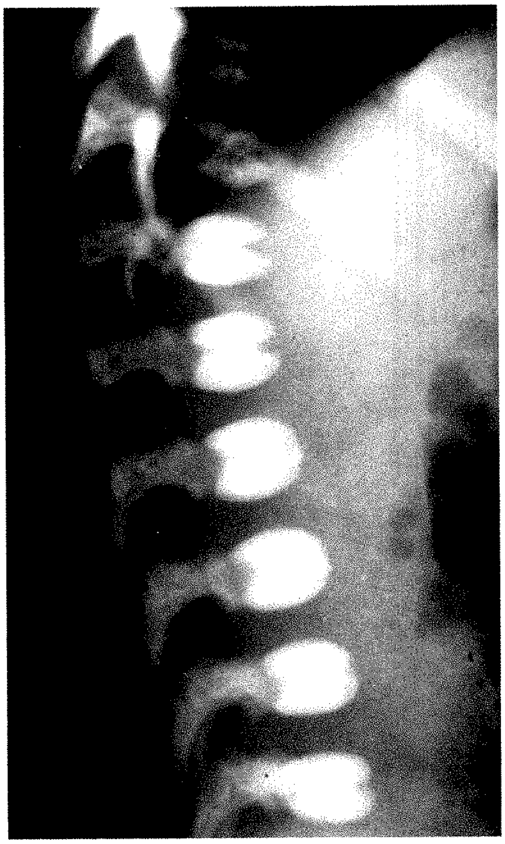

Fig. 1. Newborn child with oval vertebrae showing the anterior indentations from the intersegmental arteries.

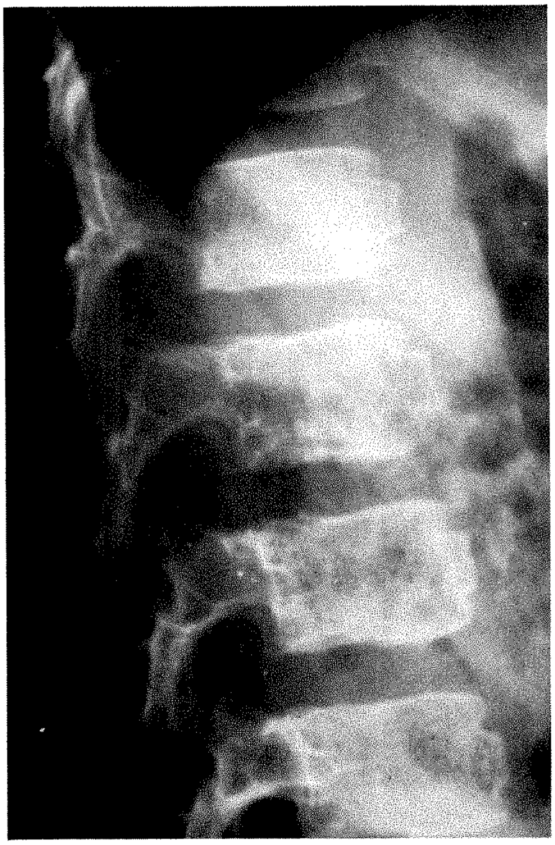

Fig. 2. Six year old child with step-like recesses at the superior and inferior margins of the vertebrae.

Vertebral growth in the vertical dimension takes place from the cartilaginous layers on the superior and inferior surfaces of each vertebra.[7,15,22,26,29] Columnar and palisading cartilage has been microscopically confirmed.[3] The cephalic and caudal advance of these cartilaginous surfaces is followed by progressive ossification of the vertebra.[6] Thus, the vertical growth process of the vertebral bodies is considered to be analogous to the longitudinal growth of the diaphysis of the long bones.

Controversy has persisted as to whether or not the growth from the superior and inferior surfaces of the vertebral body is equal.[27] Moser[28] has selectively injured the upper surface of one vertebral body and the

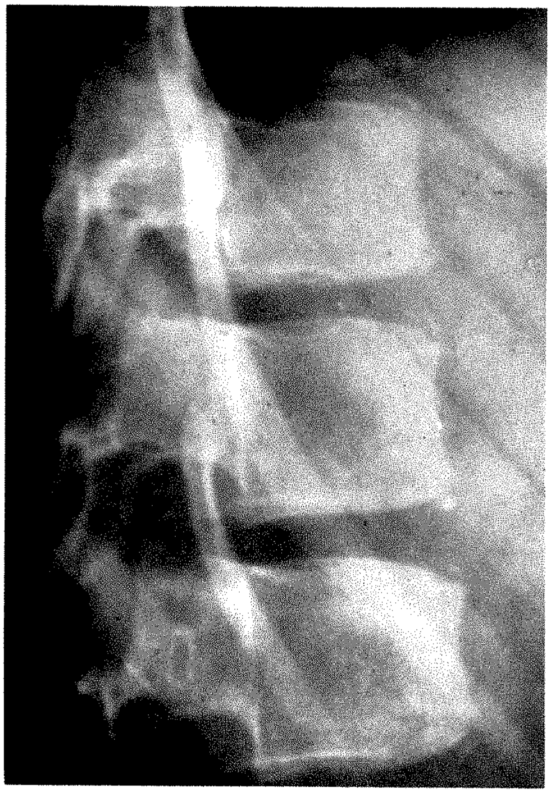

FIG. 3. Thirteen year old girl with calcification in the vertebral rim apophysis.

←

lower surface of another. He found inhibition of growth of only that vertebral body which had its upper surface damaged and concluded that growth was greater at the upper surface. However, it is uncertain that the degree of trauma was uniform at both sites.

Knutsson[21] suggests that growth is equal at both superior and inferior surfaces of the vertebral body. He points out that vestiges of the vascular groove encircling the vertebral body at its midplane may occasionally persist to adulthood and in such instances they are found to lie equidistant from the upper and lower surfaces. If growth had been greater at the superior surface, the groove in the adult ought reasonably to

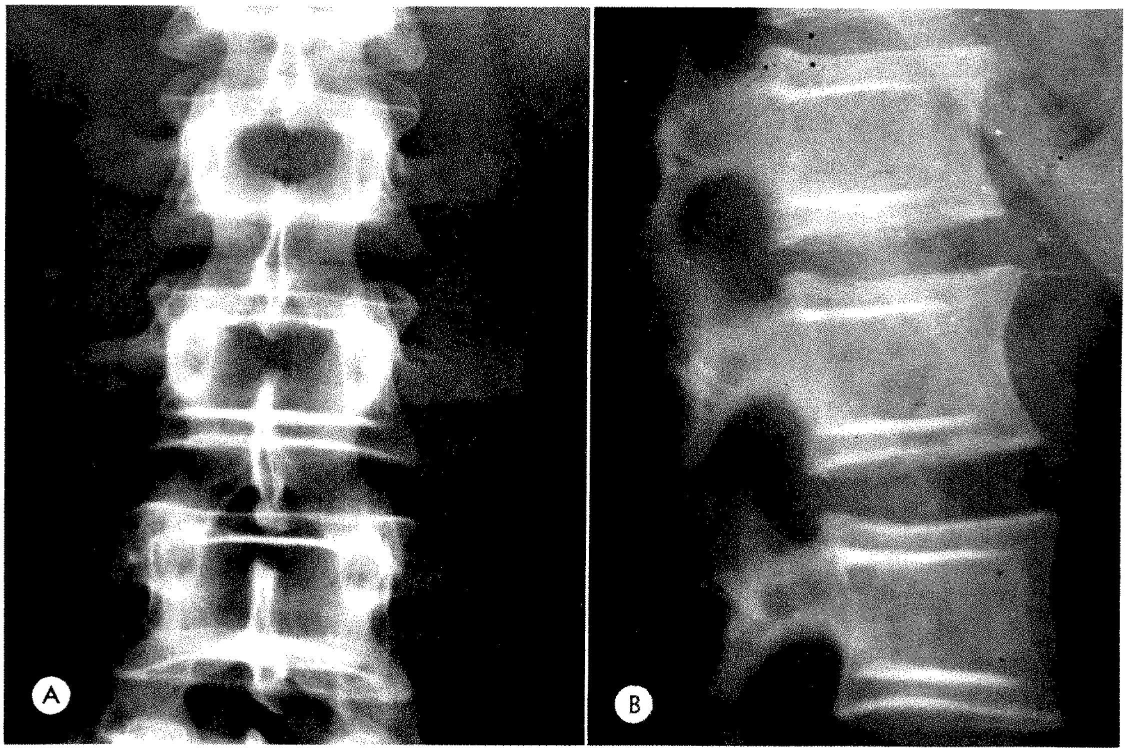

FIG. 4. (*A* and *B*) Horizontal growth disturbance lines, secondary to plumbism, equidistant from both growth surfaces indicating equality of growth at each site.

have become displaced toward the lower surface.

Conclusive evidence that equal growth occurs at both surfaces is presented in Figure 4, *A* and *B*. These roentgenograms of the lumbar vertebrae of a patient who previously had plumbism demonstrate horizontal growth disturbance lines[30] equidistant from both inferior and superior surfaces. That these lines have migrated equal distances is consonant with the theory that equal vertical growth occurred at each surface.

VERTEBRAL GROWTH IN THE ABSENCE OF NORMAL STRESS

Although all the forces that determine the ultimate size and form of an adult vertebra are not known, both intrinsic and extrinsic factors are involved. Fetal bone in tissue culture develops according to its inherent nature, but this may be modified by a variety of external influences.[32] *In vivo* studies have confirmed the susceptibility of growing bone to the effects of pressure. Pressure does not inhibit growth by an all or none law. There is no evidence of a threshold below which pressures are effective in depressing, or above which traction is effective in enhancing bone growth.[10,16]

In growing children, the vertebral response to lack of normal stress is most marked in the lumbar area because the lumbar vertebrae bear most of the weight in the normal erect posture, having phylogenetically become the largest vertebrae. Therefore, in the absence of normal vertical stress, they have the greatest capacity to respond by increasing in height.

Under the proper circumstances, increased vertebral height may be manifest early in infancy. Rabinowitz and Moseley[31] have recently reported it in infants with Down's syndrome (mongolism). We have seen it most frequently in children who have not walked for a significant portion of the vertebral growth period. Examples are children with primary nervous system disease such as amyotonia congenita, myelomeningocele, cerebral palsy, and hydrocephalus. Interestingly, decalcification or disuse atrophy of the involved vertebrae has not been observed regardless of how inactive the child has been.

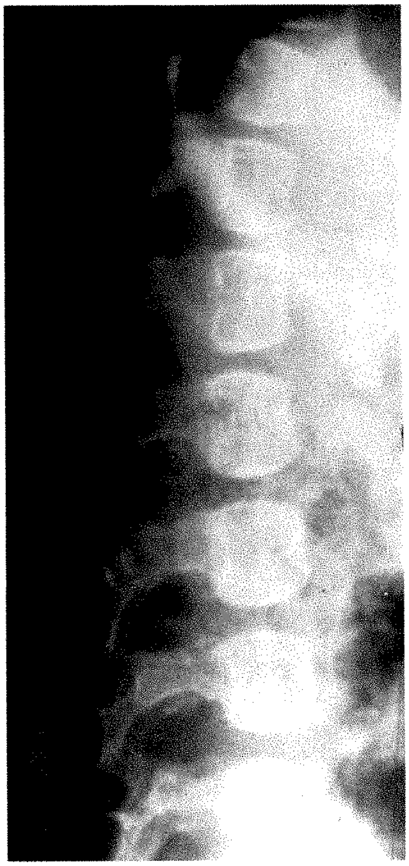

FIG. 5. This 14 month old child with Werdnig-Hoffmann disease has never sat or walked alone and consequently has vertebrae of increased height.

Figure 5 is a lumbar spine roentgenogram of a patient who had Werdnig-Hoffmann disease, an entity which results in progressive degeneration of the motor neurons. This flaccid and inactive child was unable to sit or roll over at the age of 14 months. In this case, the lack of normal weight bearing resulted in excessive vertical growth of the lumbar vertebrae.

Increased vertebral height may also be seen in older children. A lateral roentgenogram of the lumbar spine of a 4 year old boy who has never walked is shown in Figure 6. This patient, with mental and motor retardation since birth, had a tris-

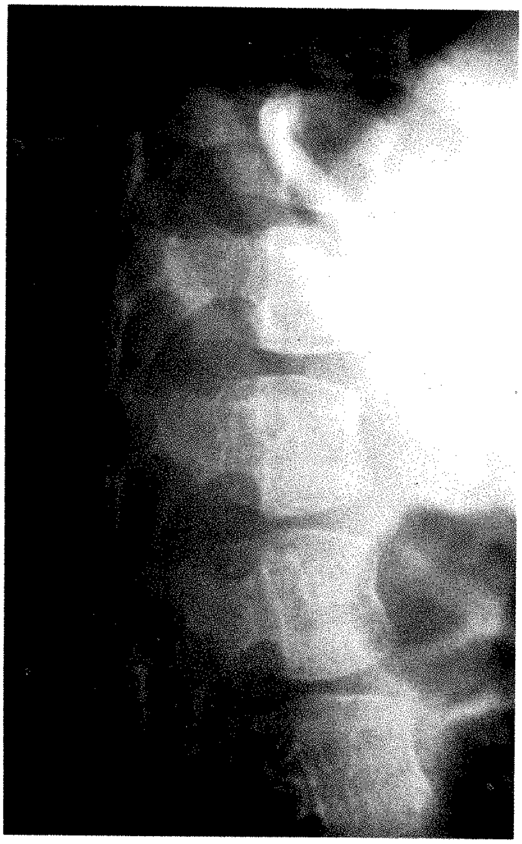

FIG. 6. This 4 year old severely retarded boy with trisomy 18 syndrome has never walked and has developed "tall vertebrae."

omy 18 chromosomal pattern. The relative increase in the vertebral height is again apparent. Another non-walker who manifested "tall vertebrae" was a 6 year old girl who had Pierre Robin syndrome and cerebral palsy; her lumbar spine is shown in Figure 7.

Another category of vertical vertebral overgrowth includes some pediatric patients with kyphosis or scoliosis. Schmorl and Junghanns[33] have noted tall vertebrae in the lordotic lumbar spine of patients with Pott's disease of the thoracic spine. They detected an increase in height of one-third greater than the usual vertical diameter.

In scoliosis, the vertical pressure is greatest on that portion of the vertebral growth surfaces closest to the concave aspect of the curve and least on the convex aspect.[9] Growth is thereby inhibited on the concave side and unrestrained on the convex side. Viewed in the lateral projection, the entire vertebra appears superficially to have increased in height; however, the anteroposterior projection resolves the ambiguities.

After posterior spinal fusions are performed on scoliotic patients, grafts are known to bend and grow as fatigue fractures develop and then heal. In this situation, vertebrae may become partially relieved of their normal weight bearing role and increased vertebral height becomes manifest (Fig. 8).

The differential diagnosis of increased vertebral height includes hemangiomata, but in these cases the vertebral circumfer-

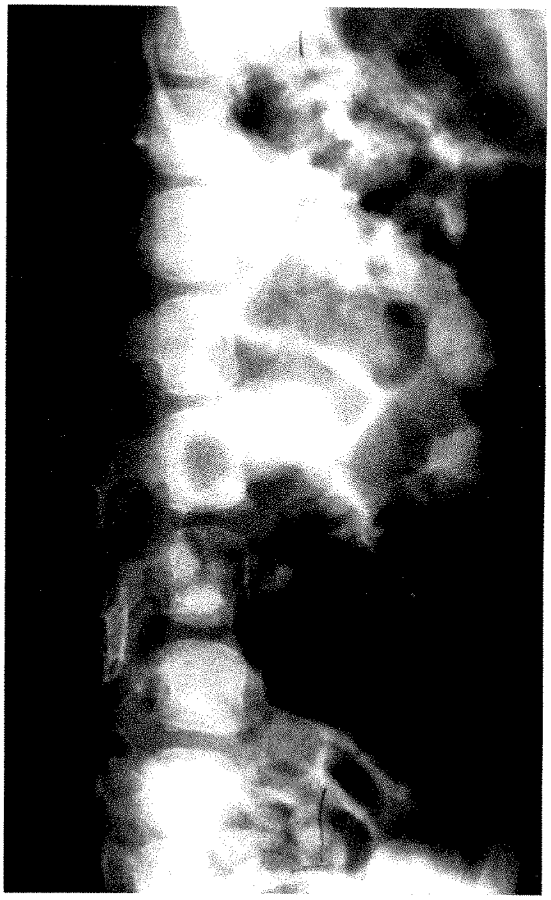

FIG. 7. Six year old girl with cerebral palsy and Pierre Robin syndrome has vertebrae of increased height.

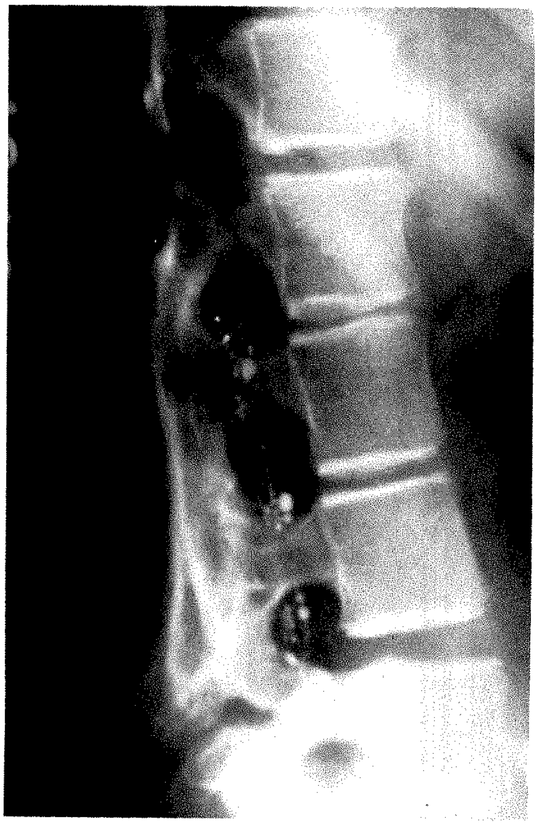

Fig. 8. This 9 year old girl had a spinal fusion and developed a pseudarthrosis. The vertebrae that had partial relief of weight bearing are of increased height.

ence is increased in addition. Fused or "block" vertebrae may simulate increased vertebral height, but usually the fusion is incomplete and, furthermore, multiple ribs, transverse processes, or articular facets lead to the correct diagnosis. Increase in the total size of the vertebra may be found in polyostotic fibrous dysplasia, Paget's disease, metastatic hypernephroma, or lymphogranulomatosis.[25] These are usually readily distinguished from pure vertical overgrowth.

Finally, it should be mentioned that development of vertebrae with a relative increase in their height is a reversible phenomenon during the growth period of the spine. If normal stresses and pressures become manifest, the affected vertebrae resume their normal proportions.[14]

SUMMARY

Vertebral bodies are derived from mesenchyme which subsequently undergoes chondrification and ossification. Vertebral growth in the vertical dimension takes place on the superior and inferior surfaces of each vertebra and is equal at both of these surfaces. In the absence of the normal stresses of weight bearing during a child's growth, increased vertical height of the vertebral bodies becomes manifest.

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Vol. 93, No. 2

MULTIPLE MANUBRIAL OSSIFICATION CENTERS IN MONGOLISM

By JOHN W. HORNS, M.D.,* *and* BERNARD J. O'LOUGHLIN, M.D.
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THE clinical diagnosis of mongolism (Langdon-Down or Down's syndrome) is often difficult and too often tragically late. Karyotype analysis of leukocyte cultures is time-consuming and occasionally misleading. Roentgenologic assistance in the early diagnosis is still welcomed eagerly. It is particularly helpful in raising the possibility in a baby otherwise not suspected of mongolism.

Several skeletal abnormalities have been described in association with mongolism, including changes in the skull, pelvis, hands, and feet. We have noted an abnormality of the sternum in the majority of mongols seen at our hospital.

In mongols there is brachycephaly with hypoplasia of the nasal bones, upper maxilla, and sphenoid.[4] Spitzer and Robinson[6] reported absence of the frontal sinuses in 26 out of 28 mongols. The middle and terminal phalanges of the fifth digits are frequently hypoplastic in mongols.[3] The mongoloid pelvis in infancy has flattened acetabular slopes, flared ilia, and slender, tapering ischial rami.[1] Extra manubrial ossification centers can be added to this list.

Ossification of the manubrium of the sternum usually begins in a single center about the sixth month of intrauterine life. Occasionally, accessory manubrial ossification centers are added.[5] If there are two centers in the manubrium, they may lie beside each other or may lie one above the other. In the second instance, the separate centers are visible on a lateral roentgenogram of the chest.

ROENTGEN FINDINGS

We reviewed the records of all mongoloid children who were hospitalized at UCLA from July, 1955 through June, 1963. There were 43 of whom satisfactory lateral chest roentgenograms had been obtained. The number of ossification centers, lying one above the other, in the manubrium was recorded. There was one center in 11 children, two centers in 29 children, and three centers in 3 children. In 33 of the children roentgenograms had been obtained from the ages of 1 month through 4 years, and 29 of these children demonstrated multiple ossification centers in the manubrium. Of 4 mongoloid children examined under the age of 1 month, 1 had two ossification centers and 3 had only one ossification center. One of these 3 children was examined again at the age of 6 months and had developed an accessory ossification center in the manubrium.

Ten mongoloid children were examined between the ages of 5 years and 9 years. Three of these had two ossification centers in the manubrium and 7 had a single manubrial center. Prior studies were available of 2 of the 7, and each of these demonstrated two centers in the manubrium on the earlier roentgenograms. These centers had fused into a single center by the age of 4 years in one child and by the age of 6 years in the other. This study indicates that the optimum age of demonstration of multiple ossification centers in the manubrium of mongoloid children is from the age of 1 month through 4 years.

Most of the mongols in our series had congenital heart disease of various types. Development of extra manubrial ossification centers could have been associated with development of heart defects. It seemed necessary to examine this possibility. Therefore, two control groups were chosen. One group had neither congenital heart disease nor mongolism. The second

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* Fellow, American Cancer Society.

TABLE I

NUMBER OF MANUBRIAL OSSIFICATION CENTERS IN CHILDREN AGED 1 MONTH THROUGH 4 YEARS

No. of Manubrial Ossification Centers	Nonmongols									Mongols
	Without Heart Disease	Ventricular Septal Defect	Atrial Septal Defect	Patent Ductus Arteriosus	Tetralogy of Fallot	Truncus Arteriosus	Transposition of the Great Vessels	All Heart Disease	All Nonmongols	
1	43	13	26	16	14	11	10	90	223	4
2	7	4	0	4	3	2	3	16	39	26
3	0	0	0	0	0	0	0	0	0	3
Total	50	17	26	20	17	13	13	106	262	33
Per Cent of Patients with Multiple Manubrial Centers	14	23	0	20	16	14	21	15	15	88

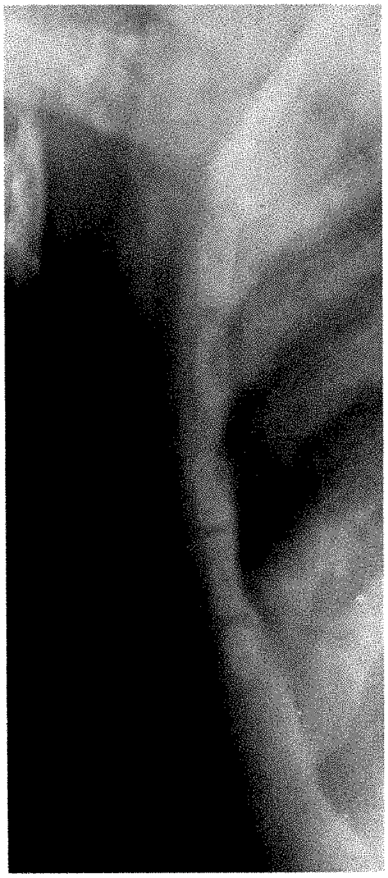

FIG. 1. Two manubrial centers, which is the usual finding in a mongol infant.

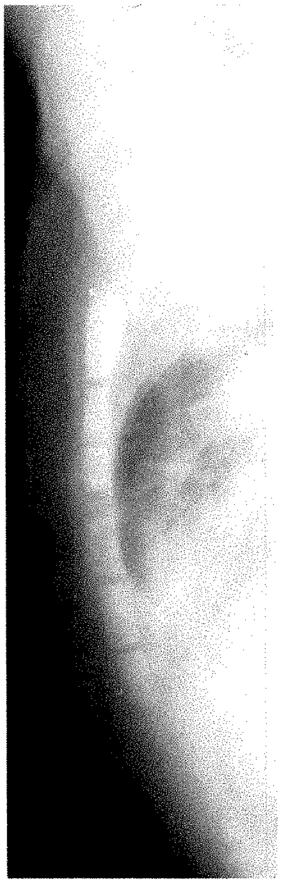

FIG. 2. Three manubrial centers in a mongol infant.

group of nonmongoloid children had various kinds of congenital heart disease, proved by cardiac catheterization, operation, or postmortem examination. The results are shown in Table I.

DISCUSSION

Currarino and Swanson[2] recently reported two manubrial ossification centers in 90 per cent of 30 mongoloid children under the age of 5 years, and in 20 per cent of 100 nonmongoloid children in the same age range.[6] In 33 mongoloid patients between the ages of 1 month and 4 years, we found 26 patients with two manubrial centers, and 3 patients with three manubrial centers (88 per cent incidence of multiple manubrial centers). Under the age of 1 month and over the age of 5 years, the incidence of multiple manubrial centers in mongols appeared to be lower. In some cases, the accessory ossification centers in the manubrium did not appear until after birth. After the age of 5 the multiple centers may fuse leaving no residual changes and a normal-appearing manubrium.

Most of the mongols in our series had congenital heart disease. However, in nonmongols there was no significant increase in the incidence of double manubrial centers in those who had congenital heart disease. Double manubrial centers occurred in approximately 15 per cent of the control groups; there was an interesting lack of this finding in 26 patients with atrial septal defect. Most commonly there were two centers of equal size (Fig. 1) and occasionally three centers (Fig. 2). Sometimes the lower center was smaller (Fig. 3) and some-

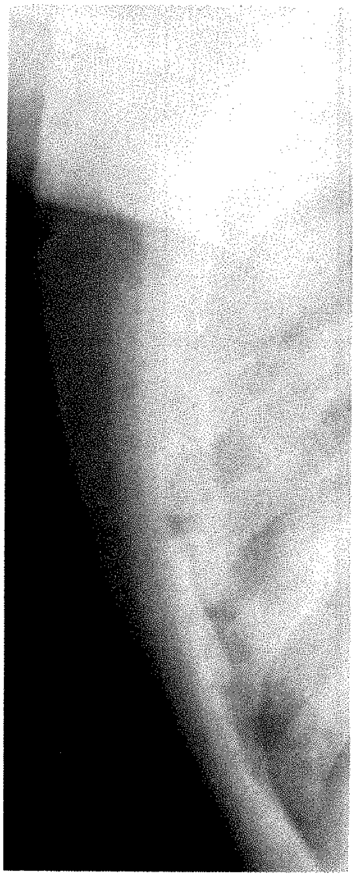

Fig. 3. Two manubrial centers of unequal size in a mongol infant.

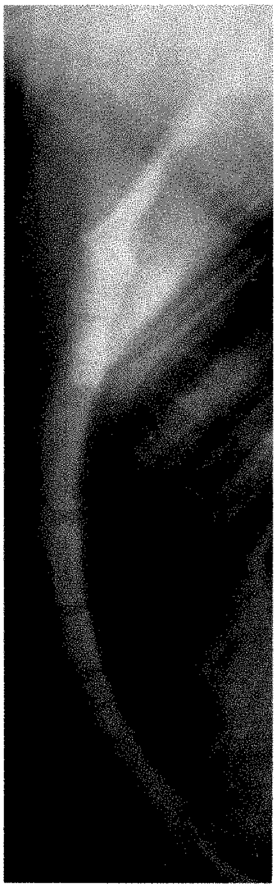

Fig. 4. Two manubrial centers, closely spaced, in a mongol infant.

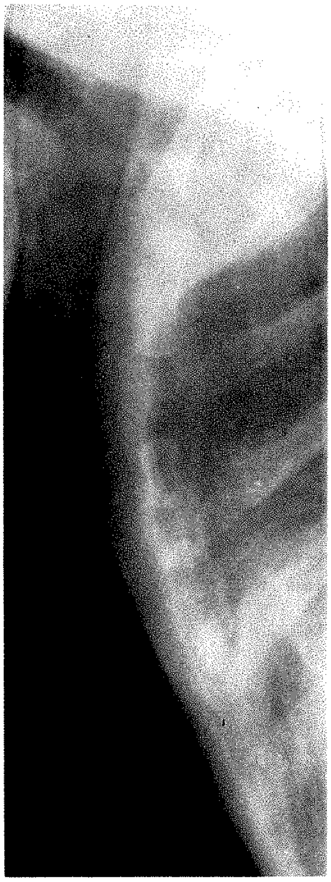

Fig. 5. Single manubrial center in a normal infant.

times the centers were partially fused so that only a thin cleft was visible in the manubrium (Fig. 4). Figure 5 shows a normal manubrium with a single center.

SUMMARY

Two, and occasionally three, ossification centers were demonstrated in the manubrium of the sternum in approximately 90 per cent of mongols between the ages of 1 month and 4 years. The multiple centers lie one above the other so that they are visible on the lateral chest roentgenogram. Two manubrial ossification centers were found in approximately 20 per cent of the nonmongol control groups. There was no significant relationship to congenital heart disease.

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DIASTROPHIC DWARFISM IN EARLY INFANCY

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DIASTROPHIC dwarfism is a recently described condition, characterized by short limbed dwarfism, club feet, distinctive deformity of the hands and external ears, progressive scoliosis sometimes combined with kyphosis, limitation of mobility and a tendency to subluxation and dislocation of many joints, most commonly the hips. It is not associated with mental retardation. The condition is hereditary with an autosomal recessive mode of transmission. The roentgenologic and clinical features in late infancy and childhood have been well described and illustrated in articles by Taybi[8] and Stover, Hayes, and Holt.[7] The latter authors state that the clinical and roentgenographic picture at birth or shortly thereafter is characteristic, and they briefly describe the roentgenographic appearance in early infancy in 1 of their cases but do not include roentgenograms made the first 6 months of life.

This entity is confused clinically in infancy with two other conditions, achondroplasia and arthrogryposis multiplex congenita. In these conditions, unlike diastrophic dwarfism, involvement in subsequent children would not be expected. (Arthrogryposis multiplex congenita is not a hereditary condition, and an achondroplast born to normal parents is a mutant.) The dwarfism in diastrophic dwarfism is marked and the skeletal deformities may be severe and are not satisfactorily correctable by presently available orthopedic techniques. The prognosis for life is good beyond the first few months where there is increased mortality.[4–8] Because of the hereditary nature and severe disability associated with this condition, it is of practical value to establish the correct diagnosis early and apprise the parents of the prognosis and the likelihood of subsequent children being affected. The combination of characteristic clinical and roentgenographic features allows an unequivocal diagnosis in early infancy.

In this report the roentgenographic appearance in 2 affected infants examined at ages 1 month and 4 months, respectively, and an associated cervical spine deformity which was symptomatic in one of the patients are illustrated. Both of the cases of diastrophic dwarfism on which this report is based, a girl now 10 years old who was first roentgenographically examined at the age of 1 month and a boy now 9½ years old who was first roentgenographically examined at 4 months of age, are severely handicapped by their deformities. The girl has kyphoscoliosis, bilaterally dislocated elbows, hips, and knees and persistent club foot deformity, all of which have been resistant to orthopedic management. The boy, in addition to hand and feet deformities, has paralysis of the lower extremities and paresis of the upper extremities due to cervical cord damage from a combination of a fall and severe developmental cervical spine deformity. He has a marked progressive kyphosis in the upper cervical spine with malformed vertebrae C3–6 and dislocation of C2 on C3 so that the tip of the odontoid is parallel to the foramen magnum (Fig. 1). Similar but less marked changes were present in Kaplan and co-workers'[3] patient, and Stover *et al.*[7] reported "a peculiar kyphosis of the cervical spine" on roentgenograms in early infancy in 1 of their patients.

REPORT OF CASES

Case 1. A 1 month old white female was admitted to the Gillette State Hospital for Crippled Children for evaluation and treatment of multiple congenital deformities. She was born at term on December 29, 1953 following an uncomplicated pregnancy. The father, 47 years old, and the mother, 46 years old, were unrelated. There was one normal brother, age 2½ years. There have been no subsequent children.

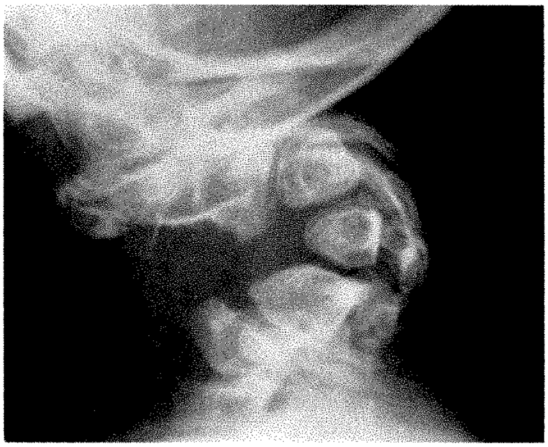

Fig. 1. Case II. Aged 8¾ years. The individual vertebrae C3–6 are malformed with kyphosis of the upper cervical spine and dislocation of C2 on C3. The long axis of the odontoid lies parallel to the foramen magnum.

No family history of congenital anomalies was elicited. The patient was alert and well nourished on admission, weighing 8 pounds, 8 ounces and was 19½ inches long. The extremities were short in relation to the trunk. There was limitation of motion of the shoulders and deformity of the hands with short fingers, extension contractures of the interphalangeal joints of the fingers and hypermobility of the thumbs. Limitation of motion of the hips and bilateral equinovarus deformity of the feet were present. There were cystic masses in the anthelix region of both ears, larger on the left than on the right. These had been aspirated in the immediate newborn period. (Fig. 2). The roentgenographic findings (Fig. 3; and 4, *A* and *B*) are summarized later in this report. A diagnosis of arthrogryposis multiplex congenita was made.

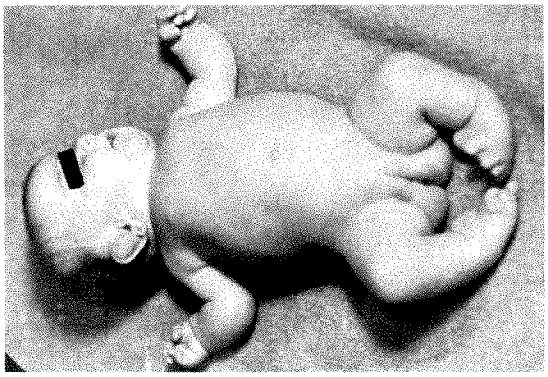

Fig. 2. Case I. Aged 1 month. The head is normal except for cystic mass in anthelix of external ear. The extremities are short with hypermobile thumbs and extension contractures at the interphalangeal joints of the fingers. There is equinovarus deformity of the feet.

Case II. A 4 month old white male was admitted to Gillette State Hospital for Crippled Children for evaluation and treatment of multiple congenital deformities. He was born at term on May 13, 1954 following an uncomplicated pregnancy. The father, 20 years old, and the mother, 19 years old, were unrelated. There was no family history of congenital anomalies. Subsequently, 2 normal brothers were born. The patient was alert and well nourished on admission, weighing 14 pounds, 8 ounces and was

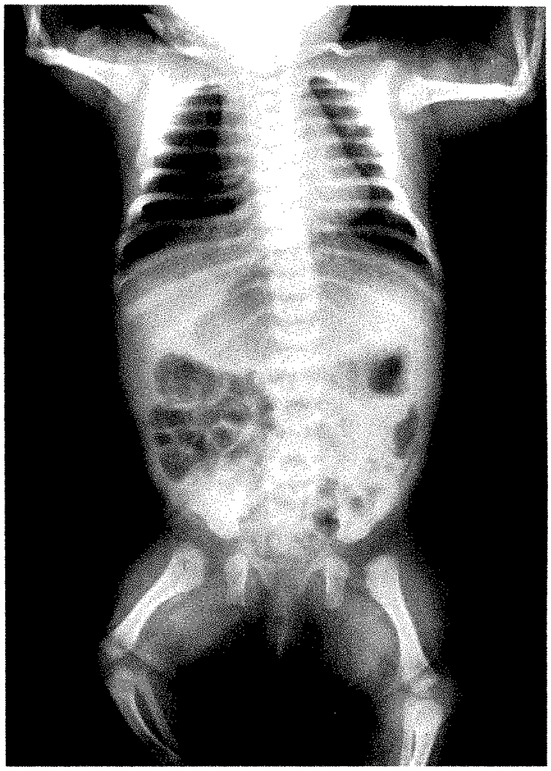

Fig. 3. Case I. Aged 1 month. Dislocation of the radii, absence of narrowing of the interpedicular distance from the upper to lower lumbar spine and normal basal portions of the innominate bones. No convincing scoliosis. Distal femoral epiphyses ossified but smaller than proximal tibial epiphyses. Short fibulae. Normal muscle mass in extremities. Metaphysial flaring of tubular bones not optimally visualized because of projection.

22½ inches long. The extremities were short in relation to the trunk. There was ulnar deviation of the hands with short fingers and hypermobility of the thumbs. Moderate equinovarus deformity of the feet was present. The ears were deformed, especially in the region of the antitragus where there was thickening, but no cystic areas were present (Fig. 5). On questioning, the patient's parents stated that in the newborn period there were soft swellings on both ears which had spontaneously resolved leaving the deformity seen at 4 months. The deformity of the external ears at age 9½ years was almost inapparent. Roentgenograms were obtained (Fig. 4 *C;* 6; and 7, *A* and *B*), and the findings are summarized later in this report. A diagnosis of achondroplasia with club feet was made.

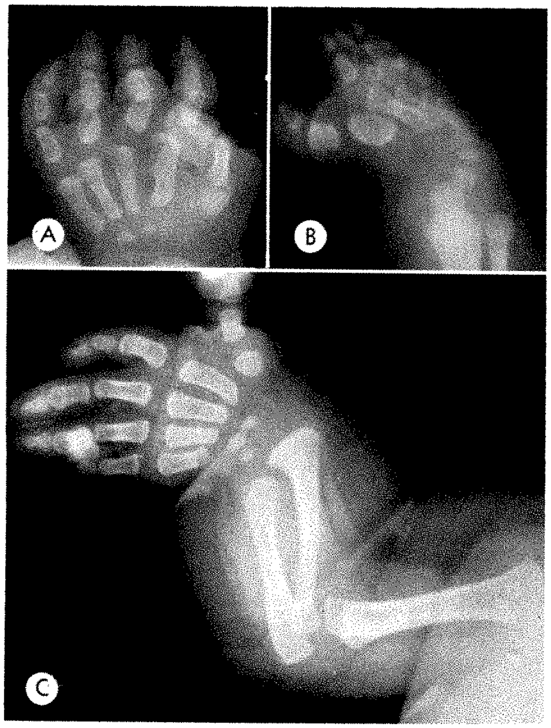

Fig. 4. Case I. Aged 1 month. (*A*) The first metacarpal is oval shaped and hypoplastic. Metacarpals 2 through 5 are short with broad distal ends. The carpal ossification is accelerated. (*B*) The first metatarsal is oval shaped. There is equinovarus deformity of the foot.

Case II. Aged 4 months. (*C*) The humerus, radius and ulna are short. There is ulnar deviation at the wrist. The hand changes are the same as in Case I. Note the normal muscle mass in the upper extremity. All of the changes were bilateral in both the hands and feet.

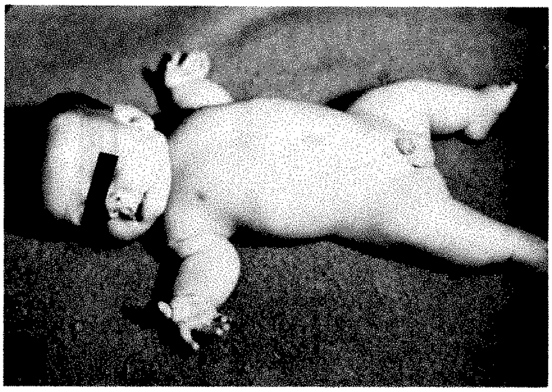

Fig. 5. Case II. Aged 4 months. The head is normal except for some deformity of the external ear not well seen on this photograph. The extremities are short with ulnar deviation at the wrists. The thumbs are hypermobile and the fingers contracted in extension at the interphalangeal joints. There is equinovarus deformity of the feet.

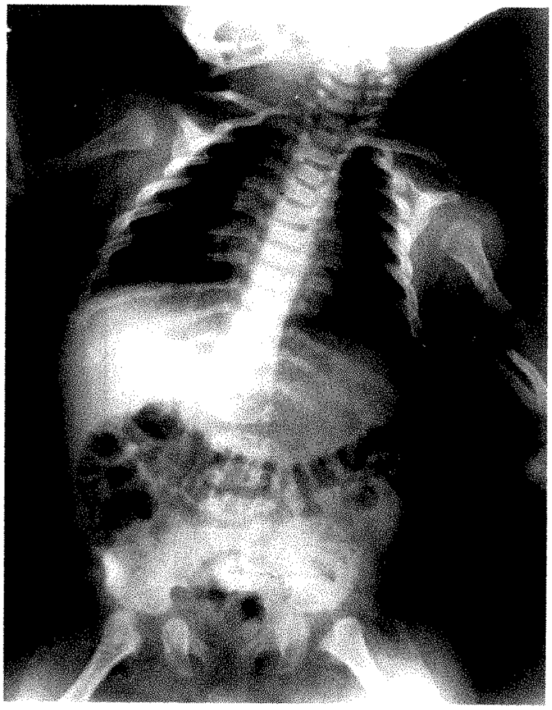

Fig. 6. Case II. Aged 4 months. There appears to be mild deformity of the upper cervical spine. The tubular bones are short with broad metaphyses. There is no change in the interpediculate distance from the upper to lower lumbar spine. The short basal portions of the innominate bones are partially due to projection (roentgenograms at older ages do not show absence of this portion as in achondroplasia). No convincing scoliosis.

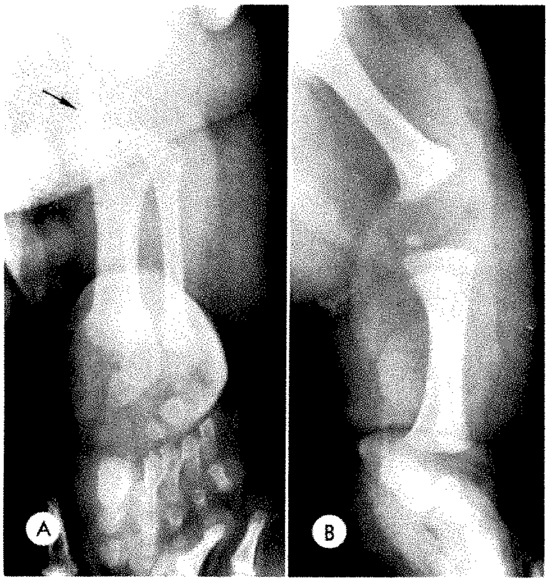

Fig. 7. Case II. Aged 4 months. (*A* and *B*) The tubular bones of the lower extremity are short with broad metaphyses. The distal femoral epiphysis is not ossified. The proximal tibial epiphysis is medially placed on the metaphysis. The changes in the foot are less marked than in Case I and partially corrected by manipulation. Note the normal muscle mass in the lower extremity.

SUMMARY OF CLINICAL FINDINGS

The clinical findings in early infancy as noted in the above 2 cases and from the descriptions of the infantile cases recorded in the literature are as follows: The extremities are short in relation to the trunk. The hands may be ulnar deviated at the wrist. The fingers are short. Extension contractures of the interphalangeal joints of the fingers are frequently present and hypermobility of the thumbs has been a constant feature. There is equinovarus deformity of the feet. Soft blister like masses on the external ear are present in the newborn period. These resolve spontaneously leaving deformity of the cartilage. In a number of cases there have been limitations of mobility in the shoulders, elbows and hips. Hypermobility of the knees has been described. Approximately one-half of the cases have cleft palates.

SUMMARY OF ROENTGENOGRAPHIC FINDINGS

The roentgenographic findings in early infancy based on the 2 above cases and the partial descriptions of Catel,[1] Duken,[2] and Stover *et al.*[7] are as follows: The most characteristic changes are in the bones of the hands and feet, particularly the hands. The first metacarpal is small and oval shaped. The other metacarpals are broad with the distal end wider than the proximal end. The proximal and middle phalanges may be broader than normal. The first metatarsal is also somewhat oval shaped and abnormally broad in relation to the other metatarsals. More carpal and tarsal centers are ossified than is normal. Equinovarus deformity is present sometimes with additional varus of the great toe. The large tubular bones of the extremities are short and have broad metaphyses. The distal femoral epiphysis, if ossified, is flattened and the proximal tibial epiphysis is larger than the distal femoral epiphysis and medially placed on the broad tibial metaphysis. The bony pelvis appears short and broad with slight flaring of the iliac wings. A definite basal portion of the innominate bones is present. In the spine the interpediculate distance increased from the level of L1 to L5 as in normal infants in 1 patient and remained the same in the other patient. The narrowing was not as marked as in achondroplasia. Scoliosis is not present in early infancy. Available roentgenograms do not allow accurate evaluation of the cervical spine although some deformity was present in Case II.

DISCUSSION

The combination of the distinctive changes in the bones of the hands and feet is characteristic and not seen in any other condition. Clinically, achondroplasia and arthrogryposis multiplex congenita may be considered. The pelvic configuration in infantile diastrophic dwarfism is somewhat suggestive of achondroplasia. However, in achondroplasia there is absence of the basal portion of the innominate bones so that these bones appear square on frontal roentgenograms. Due to the distinctive narrowing of the proximal femora in achondroplasia, there is an oval or square-shaped lucency in this portion of the bone as seen in frontal projection. The narrowing of the interpediculate distance from L1 to L5 is more marked in most cases of achondroplasia than in diastrophic dwarfism. In lateral projection, the pedicles are short throughout the lumbar region in achondroplasia (Fig. 8, *A* and *B*). This change is seen only at the L4-5 level in diastrophic dwarfism at an older age. No lateral spine roentgenograms are available in early infancy in diastrophic dwarfism, but undoubtedly this relationship would hold true at this age as well. The roentgenographic sine qua non of arthrogryposis multiplex congenita, marked decrease in the muscle mass, is not present in infantile diastrophic dwarfism (Fig. 9, *A* and *B*).

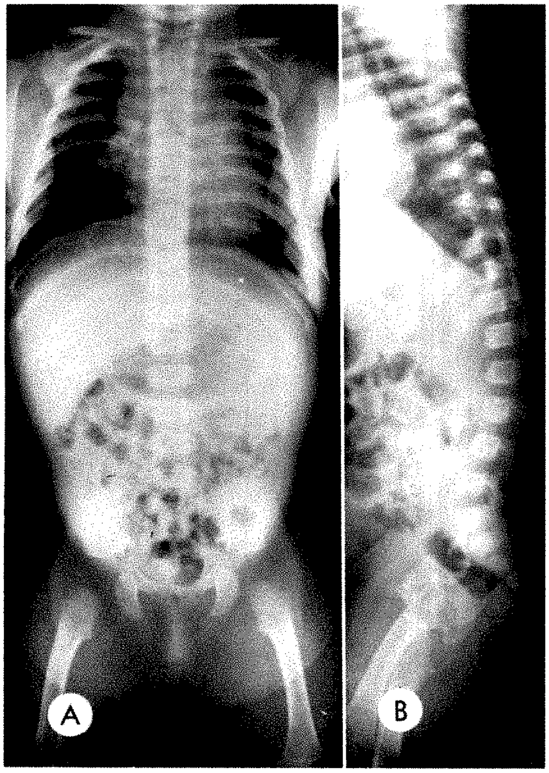

Fig. 8. Achondroplastic infant. Aged 3 months. (*A*) The interpediculate distance narrows from the upper to lower lumbar spine. The basal portions of the innominate bones are absent. The proximal femora have an oval relatively lucent appearance. (*B*) The pedicles are short throughout the lumbar spine in lateral projection.

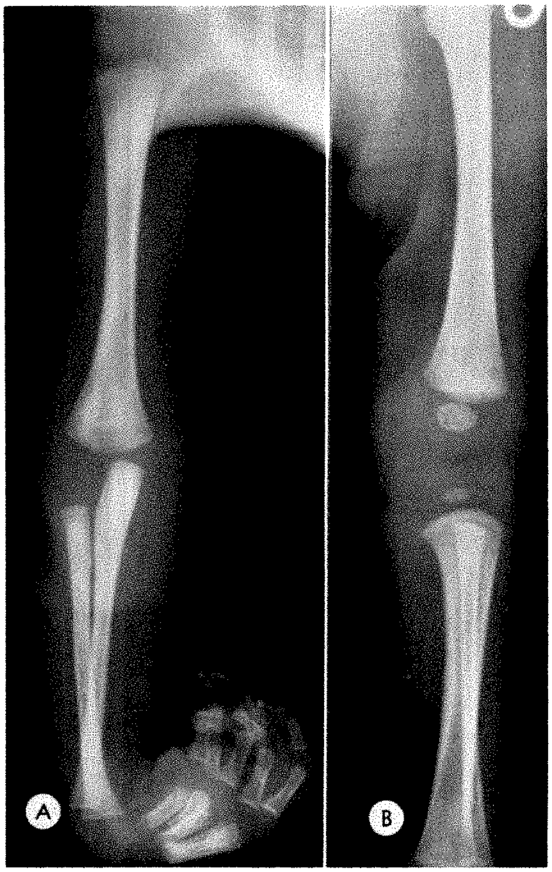

Fig. 9. Infant with arthrogryposis multiplex congenita. Aged 2 months. (*A* and *B*) The muscle mass in the extremities is small, and there is flexion contracture at the wrist. The bones are normal.

SUMMARY

Two cases of disatrophic dwarfism were examined in early infancy. The clinical and roentgenographic features of this condition in the first 6 months of life based on these cases and on available data from other early infantile cases reported in the medical literature are summarized. A progressive cervical kyphosis in one of the patients contributed to virtually a quadriplegia in late childhood.

Diastrophic dwarfism is a distinct entity. It is important to establish the correct diagnosis early in life because of the hereditary nature of this condition and the severe deformity associated with it. The clinical findings in early infancy of short limbs, cystic swelling of the external ears in the

newborn period and characteristic deformity of the hands and feet are practically diagnostic. Roentgenographic studies which also show characteristic changes, particularly in the hands with an oval first metacarpal, differentiate diastrophic dwarfism from the two conditions which have been confused with it clinically, achondroplasia and arthrogryposis multiplex congenita.

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INTRAUTERINE OSTEOGENESIS IMPERFECTA IN ONE OF A PAIR OF TWINS*

By EMANUEL J. LEVIN, M.D.
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ONE of the most common of all severe hereditary abnormalities is osteogenesis imperfecta. This autosomal dominant trait, showing wide expressivity and considerable penetrance,[7] has been reported at all ages of life.[5] The longevity of these patients is roughly proportional to the severity of the disease and the most severely affected die *in utero* or in the neonatal period. There is a decreased birth rate in osteogenesis imperfecta, but the incidence in the general population is kept at equilibrium by mutations. It is the purpose of this report to record the occurrence of osteogenesis imperfecta as a mutation in one of a pair of twins and to comment on some of the pertinent genetic and roentgenographic aspects.

REPORT OF A CASE

E.P., a 31 year old mother of 5 normal children, was admitted to the hospital in her seventh month of pregnancy with questionable premature rupture of the fetal membranes. Two fetal hearts were heard, one at a rate of 144/min., the other 124/min. A roentgenogram of the abdomen (Fig. 1) demonstrated a twin pregnancy of approximately 7 months' duration. There was a well ossified skeleton in the fetus on the left, but on the right there was such an extreme degree of hypocalcification that the skeleton was scarcely visible, although it was nearly the same size as of its twin.

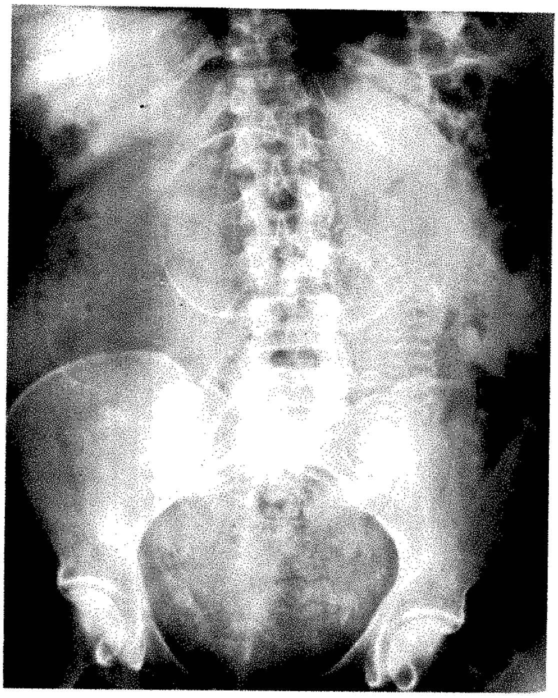

FIG. 1. Two fetal skeletons showing extreme hypocalcification of the fetus on the right.

Both fetuses were delivered by breech extraction. The first gasped several times and then died; the second succumbed 8 hours later. There were 2 amnions and 2 chorions. The fetal surface of one placenta was smooth and glistening, the other was discolored green.

At necropsy, male twin A, weighing 1,150 gm., measured 26.5 cm. from crown to rump. All physical parameters were consonant with the duration of pregnancy. The gross and microscopic examinations of the viscera and skeleton were normal for a fetus of the stated age.

Male twin B weighed 985 gm. and measured 26.5 cm. from crown to rump and 33.5 cm. from crown to heel. The crown-to-heel measurement was distinctly decreased as a result of shortening of the extremities. The head was large and soft and had the texture of a firm membrane without evidence of calvarial bones except for a few bony spicules in the temporal region. After removal of the scalp, a 5×8 cm. oval defect in the dura was seen, through which the brain was visible. The viscera were normal.

The upper and lower extremities were severely deformed and shortened, and there were numerous fractures in all stages of healing. The ribs also showed multiple fractures as well as callus formation.

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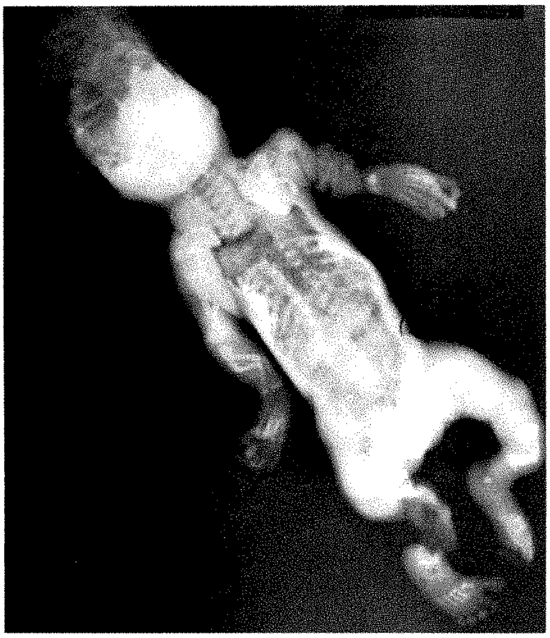

Fig. 2. Postmortem roentgenogram demonstrating multiple fractures with severe deformity.

On microscopic examination there was normal epiphyseal growth and maturation. The bony trabeculae were thin and delicate with pronounced reduction in osteoblastic activity. Callus formation was present in different degrees of maturity.

Unfortunately, the postmortem examination was performed before a roentgenographic examination could be obtained. The roentgenogram of the postmortem specimen (Fig. 2) demonstrates the multiple fractures, thin bones and shortened limbs. In another newborn infant with osteogenesis imperfecta of equal severity, the characteristic roentgen pattern (Fig. 3) is admirably demonstrated and the caput membranaceum is particularly shown to advantage.

An extensive inquiry into the genetic background of the parents disclosed no history of fragile bones, deafness, stillbirth or blue sclera. Clinical examinations and complete skeletal surveys of the parents and their 5 children demonstrated no evidence of a heritable disorder.

The conclusions were that this was an example of osteogenesis imperfecta in one of a pair of fraternal twins as a result of mutation in one of the parental germ cells.

DISCUSSION

The diagnosis of osteogenesis imperfecta[1,2,5,7] is easily established on roentgen examination in all but the mildest cases. In no other condition is there such a tendency to fracture. The presence of blue sclera or otosclerosis in the propositus or the presence of any combination of blue sclera, fragile bones or otosclerosis in the kindred is evidence confirming the diagnosis of osteogenesis imperfecta. The fetus with osteogenesis imperfecta *in utero* has been demonstrated by roentgenograms on other occasions, but the fetal skeletons were more densely calcified than in the present case and numerous fractures were obvious. One of the well-known features of osteogenesis imperfecta is the decreased calcium content of bone but calcium content of bone is difficult to evaluate on roentgen examination unless a normal standard is available for comparison. In the present case, the normally calcified fetal skeleton emphasizes the state of hypocalcification of the affected twin.

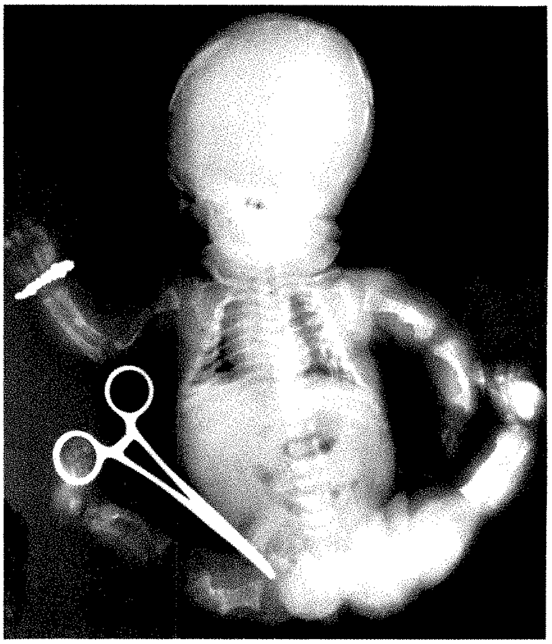

Fig. 3. Newborn infant with severe osteogenesis imperfecta. Caput membranaceum and fractures of almost every bone except the vertebral bodies are demonstrated.

On clinical examination the severely affected newborn child often presents with shortened limbs, a torso of normal size and a head slightly larger than normal. These micromelic infants bear a striking resemblance to achondroplasts and this incorrect diagnosis has been made when roentgenograms were not obtained.

The presence of 2 amnions and 2 chorions is only suggestive evidence that these twins were binovular, since in like-sexed births with duplication of amnions and chorions fraternal twins are only three times more frequent than identical twins.[11] The fact that they were discordant in respect to a heritable disorder proves the dizygous origin of the twin pregnancy: concordance would indicate the uniovular origin of the pregnancy and therefore identical twins. From the vantage of the geneticist, it is virtually certain that the occurrence of osteogenesis imperfecta in one of these twins represented a mutation.[10]

The abnormal allele of osteogenesis imperfecta is a dominant, highly penetrant trait not sex-linked or sex-limited, and the mutation could have occurred in either the parental ovum or sperm. It is characteristic of mutation that the abnormal phenotype is not found in either parent and in only one of the siblings.[10] Many of the mutations resulting in obvious effects are deleterious[9,10] and often lethal. In those cases surviving to reproductive age, the abnormal gene is transmitted exactly as is the inherited autosomal dominant gene of osteogenesis imperfecta.

In the textbook examples of osteogenesis imperfecta, survival to adult life is rarely seen. However, the majority of cases are not severe and sexual maturity is frequently attained. Even in these cases, there are complicated socio-economic and biologic factors, resulting in a decrease in the effective fertility rate.[4] Biostatisticians have shown that the incidence of the trait in the general population is constant, and that a dynamic equilibrium[10] has been established between the decreased birth rate and new mutations. In osteogenesis imperfecta the mutation rate is 4×10^{-5} per gene per generation.[6]

SUMMARY

An example of osteogenesis imperfecta in one of a pair of fraternal twins is presented. Roentgenograms taken prior to birth demonstrate severe hypomineralization of the abnormal skeleton when compared with the normal twin. A brief discussion of pertinent roentgenographic and genetic information elucidates some of the problems involved in this hereditary disorder.

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IDIOPATHIC OSTEOARTHROPATHY AND CRANIAL DEFECTS IN CHILDREN (FAMILIAL IDIOPATHIC OSTEOARTHROPATHY)*

By DONALD S. CHAMBERLAIN, M.D., JoANNE WHITAKER, M.D., *and*
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IN 1961, Currarino *et al.*[8] described a syndrome of clubbing and recurrent periosteal new bone formation with arthropathy and termed this entity "familial idiopathic osteoarthropathy." The 2 siblings concerned were also noted to have intermittent eczema, enlargement and delayed closure of the cranial sutures and fontanels, and increased perspiration of the palms and soles, but were without other disease or laboratory abnormalities. The parents and 3 older siblings were apparently healthy, and a newborn infant in the family was found to be normal.

This report concerns the subsequent development of the syndrome in the youngest sibling. In addition, an unrelated infant found to have the entity shortly after birth and followed over a 9 year period is described. These 4 children are the only documented cases of idiopathic osteoarthropathy with cranial defects we have been able to find in the literature. They also demonstrate the cranial changes which had not been recognized as part of the syndrome prior to the report by Currarino and his associates.[8]

The family reported by Currarino *et al.*[8] in 1961 was re-examined in 1963. The affected siblings, who demonstrated severe periosteal new bone formation, cranial radiolucencies, and soft tissue swelling at an early age, presented only mild residuals in the later examination. Both demonstrated clubbing of the soft tissues of the fingers. One of them, an $11\frac{1}{2}$ year old Negro female, B.S., had a small residual radiolucent defect in the left lambdoid suture and minimal abnormalities of modeling of the long bones of the extremities. Her 10 year old sister, J. S., demonstrated definite small radiolucencies in the lambdoid sutures. Chronic periarticular swelling of the knees and ankles was noted. The patient still had occasional mild episodes of joint effusion and pain, eczema, and mild fever.

REPORT OF CASES

CASE I. This 3 year old Negro female, P. S., is the youngest child of the family reported by Currarino *et al.*[8] and was born on November 15, 1960 at Cincinnati General Hospital. Physical examination was recorded as normal after particular examination because of knowledge of the affected older siblings. Roentgenographic examination of the skull (Fig. 1*A* and 2*A*) and long bones (Fig. 3*A*) was also completely normal. Significant negative findings included absence of clubbing, normal ossification of the skull and absence of periosteal elevation of the long bones. Normal laboratory values included a negative VDRL* and direct Coombs' test, and normal serum calcium, phosphorus, and alkaline phosphatase.

The patient was followed regularly in the Pediatric Clinic. She was noted to develop eczematous and seborrheic dermatitis over multiple areas of the body and, by 1 month of age, a severe degree of seborrheic dermatitis was present. Urine chromatography at that time was normal. At 6 months of age, her anterior fontanel measured 2×2 cm. in size, and by 7 months of age, 3×2 cm. Skull roentgenograms at 9 months of age (Fig. 1*B* and 2*B*) demonstrated large fontanels and a remarkable distance between the ossified portions of the occipital and both parietal bones. One month later, she exhibited definite evidence of clubbing of the fingers and toes. At the age of 2 years, the child

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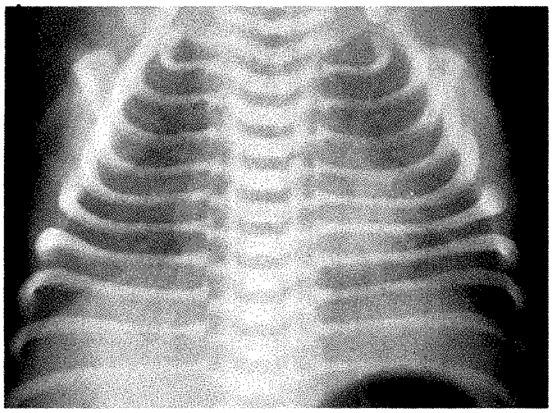

FIG. 2. Case 2. R. Roentgenogram shows finely granular reticulonodular infiltrates of lungs, air bronchogram far into lungs, peripheral lucencies, and coarse, more confluent infiltrates

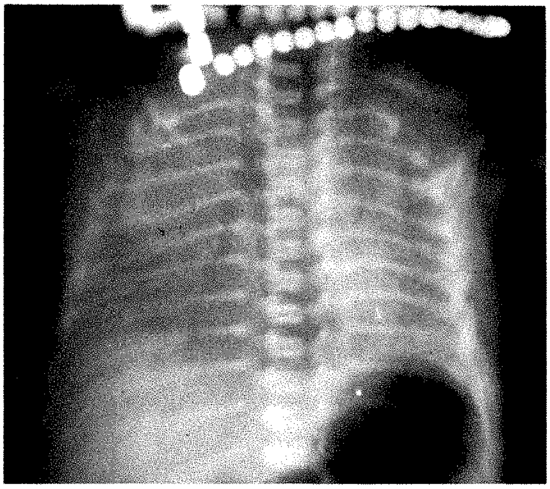

FIG. 4. Case 4. P. Roentgenogram shows finely granular reticulonodular infiltrates of lungs, air bronchogram far into lungs, coarse, more confluent infiltrates, and confluent consolidation.

confluent consolidation and/or collapse of lung.

PATHOGENESIS

There are two fundamental theories of the pathogenesis of hyaline membrane disease. One[4] is based on a deficiency of fibrinolytic activity. This theory presumes a deficiency of plasminogen-activator activity. Plasminogen is said to be activated by a substance in the lung (profibrinolysin). There may be either a lack of, or an inhibitor of, plasminogen-activator. For the production of hyaline membrane disease, there would also be required (1) coincident aspiration of amniotic fluid; (2) an alveolar effusion of blood plasma; and (3) a period of air breathing. In the absence of fibrinolytic activity, the resulting clot, which would ordinarily be liquefied and removed, might be compressed into a hyaline membrane by respiratory motion.

The other theory[1] is based on a deficiency of a substance to reduce surface tension. At birth, the lungs must expand against the

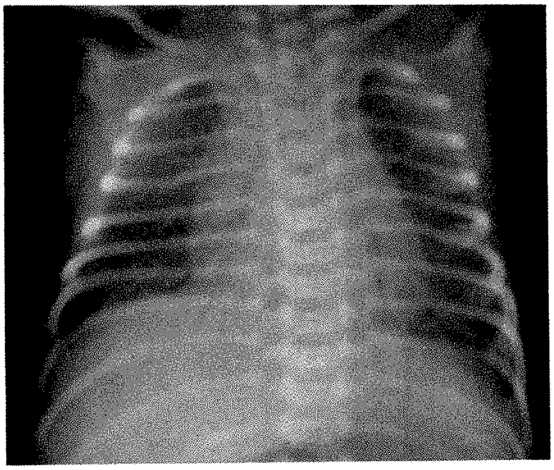

FIG. 3. Case 3. V. Roentgenogram shows finely granular reticulonodular infiltrates of lungs, air bronchogram far into lungs, and coarse, more confluent infiltrates.

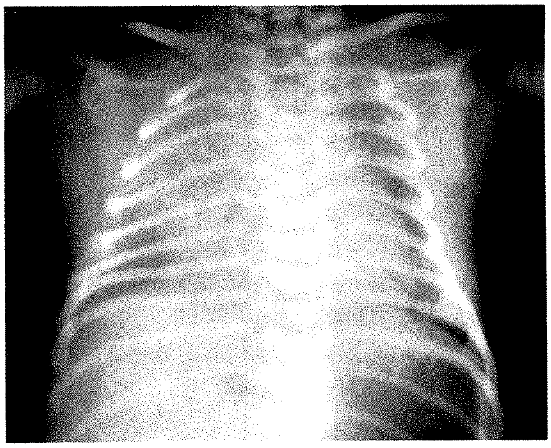

FIG. 5. Case 5. C. Roentgenogram shows finely granular reticulonodular infiltrates of lungs, air bronchogram far into lungs, coarse, more confluent infiltrates, and confluent consolidation.

HYALINE MEMBRANE DISEASE

By GERALD M. WOHLFELD, M.D.
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HYALINE membrane disease is one of the group of respiratory distress syndromes that occurs in the newborn. As such, the true diagnosis is difficult to ascertain without pathologic proof, which is seldom obtained in the living infant. With this in mind, the clinical and pathologic aspects of this disease are considered, the roentgenographic findings of 6 proven cases of hyaline membrane disease are reviewed, and the theories of pathogenesis are discussed.

CLINICAL AND PATHOLOGIC ASPECTS

The name "hyaline membrane disease" is derived from the histopathologic findings. There is collapse (atelectasis) of the alveoli, with the alveolar ducts frequently distended and lined with amorphous eosinophilic material.[3]

The typical case of hyaline membrane disease has its onset at $\frac{1}{2}$ to 96 hours after birth.[5] There is labored breathing, cyanosis, and retraction of the thoracic cage. The patient is usually afebrile and breathing is spontaneous. Hyaline membrane disease is never found in the stillborn. It is more frequent in premature infants than in full term infants, in infants following cesarean section than after normal delivery, and in infants of diabetic mothers than healthy mothers.

The complications of hyaline membrane disease are bronchopneumonia, hemorrhage, and immaturity of organs. Hemorrhage occurs in the following order of frequency: (1) Subarachnoid hemorrhage; (2) hematoma of scalp; (3) hemorrhage into peritoneum; and (4) hemorrhage into liver capsule. Immature development is common in liver and kidney and rare in thyroid, intestine, cerebellum and pancreas.

Death usually occurs within the first 4 days of life.

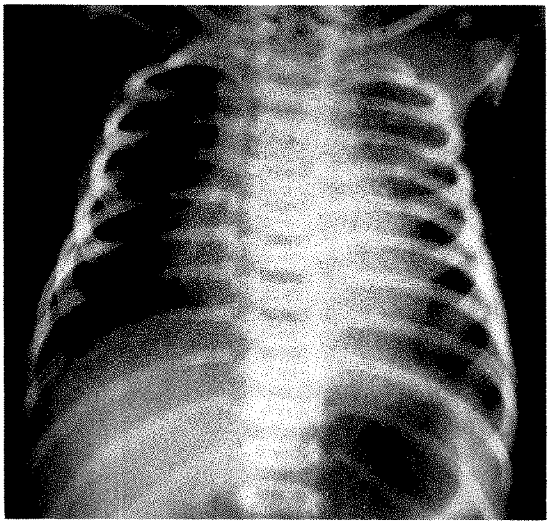

Fig. 1. Case 1. P.P. Roentgenogram shows finely granular reticulonodular infiltrates of lung, air bronchogram far into lungs, and peripheral lucencies.

ROENTGENOGRAPHIC FINDINGS

Six cases from the Department of Pathology files of Indiana University School of Medicine with proven hyaline membrane disease were reviewed as to the roentgen features. They conformed well to the above clinical and pathologic findings. The chest roentgenograms of all 6 children showed a fine reticular infiltrate throughout both lungs with air bronchogram extending well into the periphery of the lungs. Four of the 6 roentgenograms demonstrated more confluent diffuse infiltrates. Three presented finding of peripheral lucencies of the lung fields.

These roentgenographic findings (Fig. 1–5) are consistent with those previously described by other authors:[3,5] (1) Finely granular or reticulonodular increased density of lungs; (2) air bronchogram far into lung (segmental bronchi); (3) peripheral lucencies; (4) progression by coarser more coalescent type infiltrates; and finally (5) satisfactory technique by which to study the spinal canal, even in the presence of moderately severe scoliosis.

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The authors wish to thank the Moscow Clinic, Moscow, Idaho, for permission to reproduce the roentgenograms in connection with Case II.

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adjacent rib is claimed to be frequently present in such cases. This suggests local rather than segmental or general factors as the explanation of abnormal spinal curvature, contrary to some earlier opinions, and further confuses an already puzzling problem of causality of scoliosis. Hunt and Pugh[12] state that the involved vertebrae in this disorder are soft and dysplastic. The concept of the localized type of dysplasia which involves mesodermal as well as ectodermal structures is an attractive one, but proof that these vertebrae are primarily dysplastic rather than deformed secondarily is lacking.

RIB LESIONS

Rib lesions coexist with abnormal curvature of the thoracic spine in the vast majority of cases. Hunt and Pugh[12] found rib lesions associated with scoliosis in 12 of 14 cases with neurofibromatosis. In the 2 cases reported above, the rib lesions were prominent near the apex of the scoliosis in each case. This relationship was also noted in the roentgenograms of other published cases when the thoracic spine was involved.[2,7,16] The rib lesions appeared to be more prominent on the side of the convexity. One such case from the French literature is interesting in its similarity to our Case II.[9] Roentgenograms of the thorax made in infancy had shown normal ribs and very little scoliosis. Later in childhood, grotesque scoliosis had developed as had obviously related rib lesions. The cause of the rib lesions is ordinarily considered to be direct pressure from neurofibromas of intercostal nerves. Hunt and Pugh[12] report, however, that some patients with these changes have not proved to have intercostal neurofibromas at operation.

The typical deformity of the rib has been described as resembling a twisted ribbon. It always involves the vertebral end and proximal shaft of the rib. Holt and Wright[11] called attention to lesser degrees of erosion which occur in the presence of neurofibromatosis. Their report also includes a patient with a severely deformed rib in whom scoliosis was not demonstrated. We have had similar experience with other cases.

Rib lesions are ordinarily absent when scoliosis occurs independently of neurofibromatosis. The exception is the rare variety in which congenital abnormalities of both the ribs and vertebrae exist. These are roentgenographically distinctive and do not resemble the changes of neurofibromatosis.

ROENTGEN DIAGNOSIS

Positive contrast myelography has proved a satisfactory method by which to identify and localize neoplasms of the spinal cord, arachnoid cysts, and intra- and extradural neurofibromas. There are special problems with this method when spinal deformity is severe, as in the presently reported cases of neurofibromatosis. Contrast material could be collected in the concavity of the scoliotic spinal canal, but was useless in outlining the opposite convex surface. A very large volume would have been required in order to fill the dilated subarachnoid space. Air myelography, as carried out by Bunner[4] in studying thoracic lateral meningoceles, proved to be a satisfactory method of examination of the spinal canal in neurofibromatosis. Its advantages over positive contrast myelography are considerable when abnormal spinal curvature is present.

SUMMARY

1. Two cases of von Recklinghausen's neurofibromatosis are reported which show typical severe spinal curvature, extensive erosion of the bony spinal canal, and characteristic rib lesions.
2. Intraspinal neurofibromas were not found in either case roentgenographically or in the case explored surgically. The zones of bone erosion corresponded to saccular areas of dilatation of the meninges.
3. Pneumomyelography proved to be a

Recklinghausen's disease, it proves to be an inadequate explanation for the bone changes which are seen. This is demonstrated in the 2 cases above and in similar cases recorded by Hunt and Pugh.[12] In 5 instances, erosive bone changes in the spinal canal had either more extensive distribution than the contributing neurofibroma (3 cases) or had no neurofibromas whatsoever related to the bone lesions in the spine.[12] Intraspinal neurofibromata are evidently more common as isolated lesions than as part of the disease complex described by von Recklinghausen. The intradural neurofibromata produce cord compression before bone changes can be recognized roentgenographically. Extradural lesions are frequently responsible for bone erosion as they grow partly within the spinal canal and are partly protruding through an intervertebral foramen (dumbbell or hourglass tumors). According to Bull,[3] the zones of pressure erosion associated with such tumors are sharply localized. If more than 2 adjacent vertebrae are involved roentgenographically, it is very unlikely that an intraspinal neurofibroma is present in the experience of this author. Camp's[5] report confirms the frequency of associated roentgenographic spinal erosion to be somewhat less than 50 per cent.

The saccular dilatation of the meninges shown in Figure 8 apparently has the capability of producing bone erosion of a very severe degree independent of any intraspinal mass. This capability has been brought out by earlier writers, especially in connection with the appearance of a large diverticulum through an intervertebral foramen (lateral meningocele) which has been repeatedly recognized in cases of neurofibromatosis in adult patients.[8,15] Saccular dilatation of the arachnoid, either penetrating the dura or expanding it, also occurs as an independent entity.[18,20,23] This process might be a forerunner of those cases of lateral meningocele not associated with neurofibromatosis which do not have an obvious explanation in gross developmental vertebral defects. Sammons and Thomas[22] have postulated that the meningocele can produce an effect on the vertebral column resembling that of aortic aneurysm. In both aortic aneurysms and meningocele, the abnormal vessel wall or meninges allow erosion of the hard vertebral body and spare the resilient disk. It was postulated that the erosion so produced was the result of pressure caused by pulsation of the respective vessel or meningocele.

ABNORMAL SPINAL CURVATURE

This is the most common skeletal abnormality seen in neurofibromatosis, and of all cases of the disease, scoliosis can be recognized in an estimated 10 per cent.[13] Slight degrees of scoliosis are often present in patients with spinal cord tumor. Arachnoid cyst disease is more usually seen with moderate degrees of kyphosis than with scoliosis. When the spine is involved in neurofibromatosis, both scoliosis and kyphosis usually appear, but these may exist separately. Either may be mild or severe. The published roentgenograms showing spinal deformity in the cervical or lumbosacral spine indicate a preponderant kyphotic element. Thoracic vertebral deformity is more common than deformity at other levels and is more likely to be of a scoliotic variety.[10,11] The scoliosis is more acutely angular than is the case in idiopathic or paralytic scoliosis, and progression of the curvature is apt to continue beyond skeletal maturity when progression of scoliosis ordinarily stops. In cases of neurofibromatosis, as in other diseases of the spine, symptoms of spinal cord compression can develop for purely mechanical reasons when the acute angulation causes subluxation and encroachment on the spinal canal.[14,17,21]

According to a recent report, scoliosis of a similar type is occasionally seen in patients who do not have neurofibromatosis, but who have single paraspinal or foraminal tumors of neurogenic origin, particularly ganglioneuromas.[6] Erosion with enlargement of the intervertebral foramina and the

Comment. The cases described demonstrate the typical roentgenographic expression of neurofibromatosis in the spinal canal. No evidence of neurofibroma tumor masses as the cause of the roentgenographic appearance or of the scoliosis could be found. The noteworthy changes are erosion and expansion of the spinal canal, scoliosis or kyphoscoliosis and rib deformities. Each of these elements are considered separately.

VERTEBRAL EROSION

The changes in the bony spinal canal and in the intervertebral foramina which accompany neurofibromatosis have been described frequently.[1,2,10,11,16] Most of these changes are not qualitatively different from the alterations associated with neoplasms of the spinal cord or surrounding tissues. Intraspinal arachnoid cysts produce an identical appearance. The roentgenographic change usually recognized earliest in intraspinal neoplasm is slight flattening of the medial surfaces of one or more pairs of vertebral pedicles. Later, the pedicles are grossly misshaped and segmental increase in interpedicular distance is measurable. Proper projections may show thinning of the lamina, and eventually the dorsal surfaces of one or several vertebrae become misshaped with rather smoothly eroded concavity, which is referred to as "scalloping." The opinion has been expressed that the severity of changes and the number of consecutive vertebrae involved indicate the size of the intraspinal neoplasm responsible.[19] However, when this reasoning is applied to intraspinal neurofibromas in von

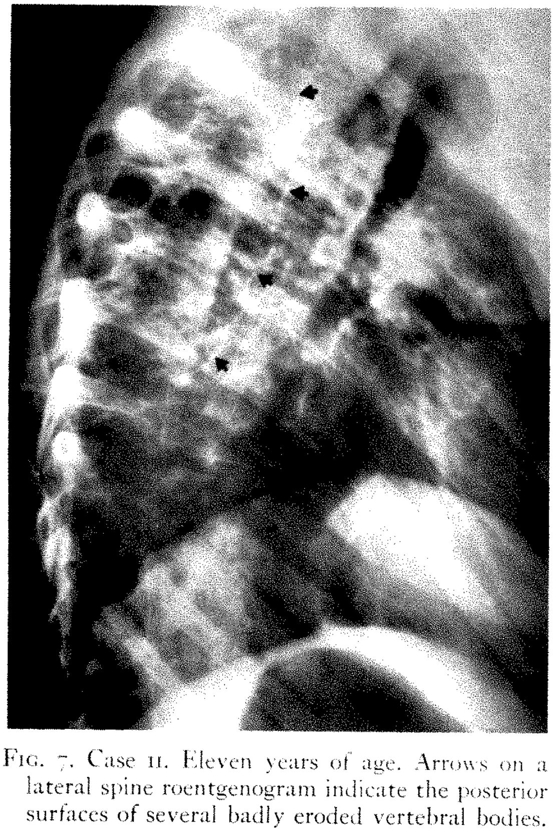

Fig. 7. Case 11. Eleven years of age. Arrows on a lateral spine roentgenogram indicate the posterior surfaces of several badly eroded vertebral bodies. The intervertebral disks are eroded less deeply by the expanding arachnoid envelope.

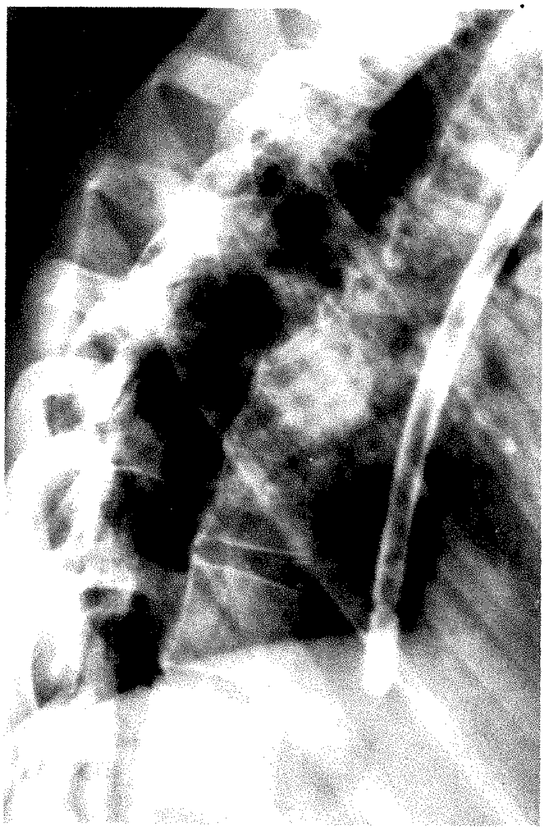

Fig. 8. Case 11. An air myelogram shows that the spinal canal contains no neurofibromas corresponding to the zones of bone erosion. The cord is posteriorly placed in the spinal canal. There is a small amount of extra-arachnoid, subdural gas inferiorly. The arachnoid matter pouches forward into the bone defects at higher levels.

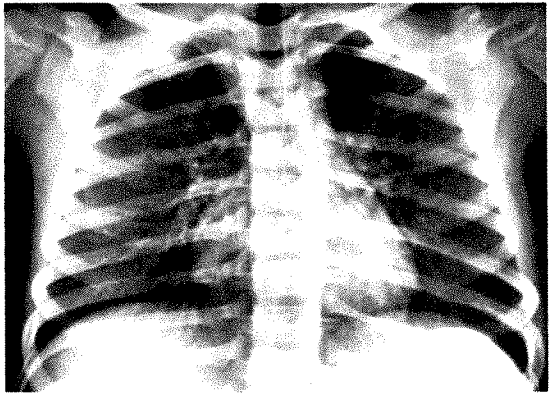

FIG. 4. Case II. Five years of age. Thoracic pedicles are abnormally shaped over at least 7 segments; however, as yet there is almost no scoliosis. The lower several pairs of ribs are mildly asymmetric.

T-9. Roentgenograms of the skull were normal.

Roentgenograms from outside sources showed earlier stages in the evolution of this deformity (Fig. 4, 5 and 6).

Pneumomyelograms made at the University Hospital demonstrated an enlarged subarachnoid space with saccular dilatations of the dura and arachnoid corresponding to erosion of the bony canal in the routine lateral views (Fig. 7 and 8). No neurofibroma masses were noted in the spinal canal. The spinal cord was of normal width placed slightly posteriorly in the spinal canal.

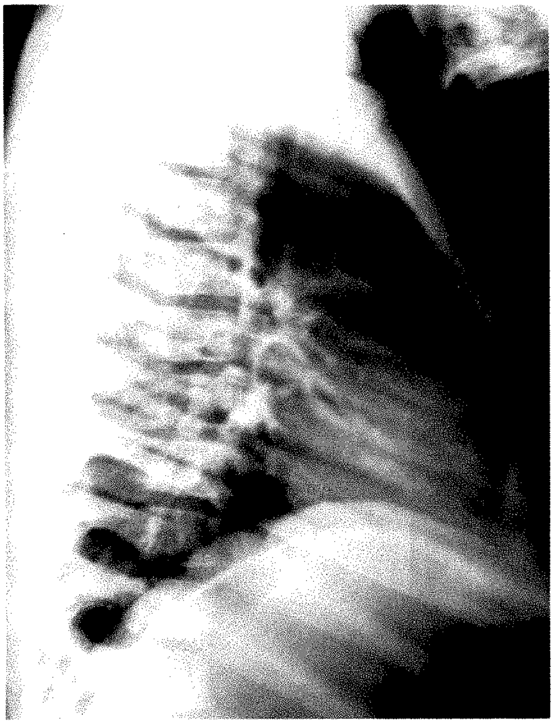

FIG. 5. Case II. Five years of age. The thoracic centra have essentially vertical posterior margins. No erosive changes can be seen as yet.

The patient was admitted to the hospital for spine fusion on June 3, 1961, with a diagnosis of neurofibromatosis complicated by scoliosis of an acutely angular variety. A two stage fusion was done. The first stage, which was performed on June 5, 1962, consisted of a fusion from D-1 through D-8. The second stage of the fusion was done on June 26, 1962, and extended from D-8 through D-12. At surgery, there was noted to be an abrupt rotation and angulation of D-6. The D-6 vertebral lamina was deformed by the acute angular scoliosis, and as a result the facet joints between D-6 and D-7 also appeared deformed. Projecting between the transverse processes at the 5th and 6th level was a round, firm nodule which was thought possibly to represent a neurofibroma. This was excised and sent for pathologic examination. It had not caused bone erosion. The biopsy showed only fibrous connective tissue without evidence of palisading.

Postoperative recovery from the 2 operative procedures was uncomplicated. On July 10, 1962, a Risser cast was applied, and the patient was discharged on July 15, 1962.

One year after surgery, the fusion was noted to be solid clinically and roentgenographically.

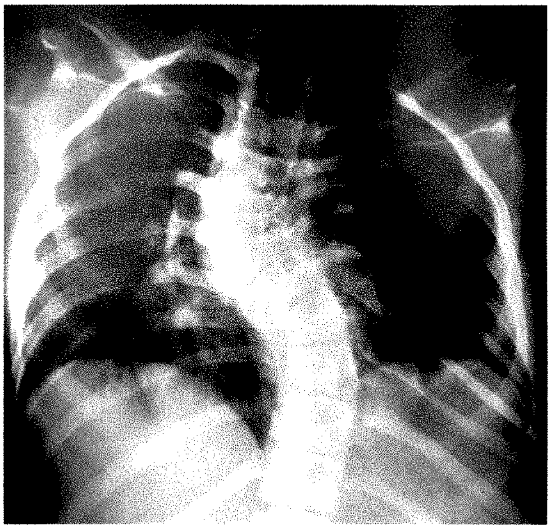

FIG. 6. Case II. Eleven years of age. A moderate thoracic scoliosis has developed. There is partial subluxation of the centrum of T-8 on T-9 and the rib abnormalities are now striking on the left.

the rate of increase in the size of the mass was in proportion to the rest of the body. The parents stated that the child had always seemed more awkward and uncoordinated than her healthy siblings. The patient was said to drag her heels somewhat when walking, to stumble frequently, and to have poor coordination of her hands and feet. However, her rate of development had been relatively normal. She sat up at 7 months, walked at 12 months, talked in 2 or 3 word sentences by 18 months, was toilet trained by 24 months, and started to school at 6 years.

The patient excelled in school work through the sixth grade, the level she had attained at the time of her first admission. She was hampered through the third grade by a speech impediment involving slurring of "s's" with some stuttering requiring special speech classes. She had never done well in physical education classes. She required more rest than her siblings, and for the past year had spent all of her out of school hours, including recesses, resting. At the age of 10½ years, the patient noted difficulty sitting up straight and complained of mild mid-dorsal back pain. A scoliosis deformity was noticed with a convexity to the right. The patient lost 1 inch in height in the subsequent 6 months. There was no history of referred pain, numbness, increased weakness, or spasticity.

Prepartum and birth histories were normal. Weight gain for the neonatal period was normal, in spite of the fact that the patient was noted to have frequent loose stools and occasionally vomited. Previous illnesses included measles, mumps, and chickenpox. She had otitis media at the age of 5 years, but had no residual hearing defect. Immunizations included 3 DPT shots, 4 poliomyelitis shots, and 1 smallpox vaccination.

The patient had had cystitis 2 years previously which was treated by her family physician. At that time there was painful dysuria and a question of hematuria. She was treated with pills and the symptoms have not recurred. She had not yet started to menstruate but pubic and axillary hair had appeared and there was early breast development.

The age of the patient's father was 46 years, and that of her mother was 47 years. Both parents were living and well. Siblings included a 4 year old sister, a 14 year old brother, and a 16 year old sister who were all living and well. The 16 year old sister had one brown area of pigmentation located on her leg. It was 7 cm. in diameter. No other abnormalities relating to neurofibromatosis could be traced in members of the family. Four maternal aunts and maternal uncles, 13 first cousins, 2 paternal uncles and 1 paternal aunt were living and well without abnormal masses or pigmentation. The mother had a brother with colitis and a grandmother and aunt with diabetes. There was no family history of tuberculosis.

At the time of initial examination, the patient was well nourished and was of grossly normal stature. She was alert and cooperative. A large 5×10 cm. soft tissue mass, which contained multiple nodular masses of firmer consistency, was located on the left posterolateral trunk over the inferior aspect of the scapula. The small, firm masses were nontender and fairly movable. The skin overlying this area had medium brown pigmentation and was covered with increased amounts of hair. There were many flat, brown spots with smooth margins, ranging in size from that of a pea to that of a 50 cent piece. These were located on the thorax, abdomen, and legs. There were no nodules of the skin other than the ones described.

The cranial nerve examination was negative. No weakness or spasticity was noted in the lower extremities. Skilled acts involving handwriting, shoe-tying, and buttoning were performed well. Finger-to-nose tests were performed well with either hand. The Romberg test was negative. There was no difficulty with rapidly alternating movements, and the tests for rebound and past pointing were normal. There was good strength and tone in all muscles. No abnormal movements were noted. Reflexes were physiologic, and no pathologic reflexes could be demonstrated except for an equivocal Babinski response on the left. No abnormalities in sensation could be demonstrated. Severe kyphoscoliosis was noted in the upper dorsal spine with convexity to the right, and moderate scoliosis was present below with convexity to the left. The left shoulder was lower than the right. There was prominence of the anterior left chest.

Roentgenograms of the thorax and spine were made in multiple projections. There was moderate scoliosis convex to the right at the T-6 level, and to the left at T-10. Ribs 6 through 9 on the left were deformed and the 4th and 5th ribs showed slight abnormalities. The levels of spinal deformity extended from T-4 through

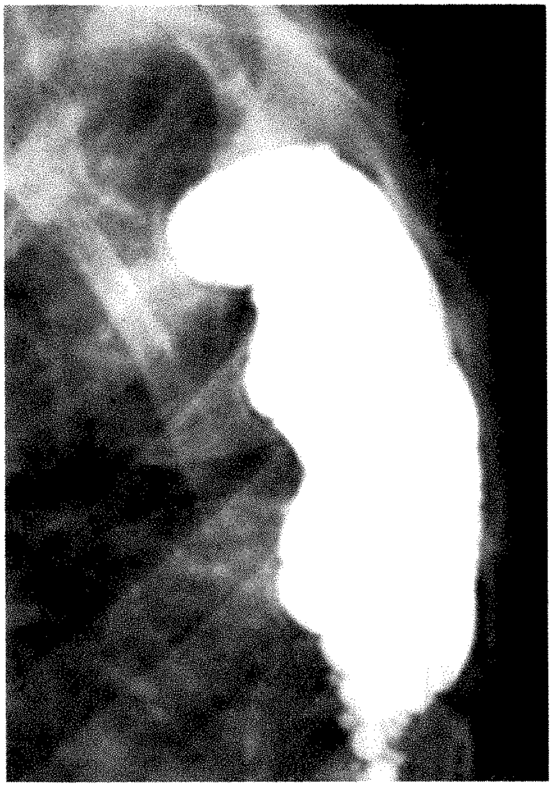

FIG. 2. Case I. Contrast material is collected in the expanded subarachnoid space at the apex of the primary scoliotic curve in the mid-thoracic spine. The eroded zones in the vertebral centra do not correspond to intraspinal masses, but rather to arachnoid sacculations.

D-3 through D-10 with the aid of Harrington spine jacks. The postoperative course was uneventful. The patient was discharged on March 2, 1960, and was afterwards seen at intervals in the Orthopedic Outpatient Department. The jacks were removed on June 29, 1961 because they had become prominent and uncomfortable. At that time the fusion appeared solid.

On November 10, 1961, the kyphoscoliosis was noted to have increased both clinically and roentgenographically. Pseudoarthrosis was diagnosed and the patient was reoperated for repeat fusion on March 18, 1962. The pseudoarthrosis at the apex of the curve was found and was repaired. The postoperative course was smooth. A Risser localizer which included the head was applied 10 days postoperatively, and the patient was discharged in this cast.

When last seen in September, 1964, the patient was ambulatory and no further advance of the curve was noted.

CASE II. J.H., an 11 year old white female, was first seen at the University Hospital on May 10, 1962, with a previously established diagnosis of neurofibromatosis. The chief complaint was of rapidly progressive scoliosis over the preceding 6 month period.

At 7 months of age, the mother of the patient noticed a quarter-sized, brown spot on the skin just above the patient's navel. Similar spots appeared in increasing numbers, until at the age of 3 years there were approximately 30 of these scattered over the trunk and extremities. They were flat, nontender, and lacked induration. After the age of 3 years the pigmented areas remained unchanged and no new ones appeared. At about $2\frac{1}{2}$ years of age, the mother noticed a chain of several subcutaneous nodules which were located posteriorly over the left rib cage in the region of the third through ninth ribs. An excisional biopsy was performed and the diagnosis of neurofibromatosis was established. At the age of 3 years the mass had increased in size to that of a fist. Subsequently,

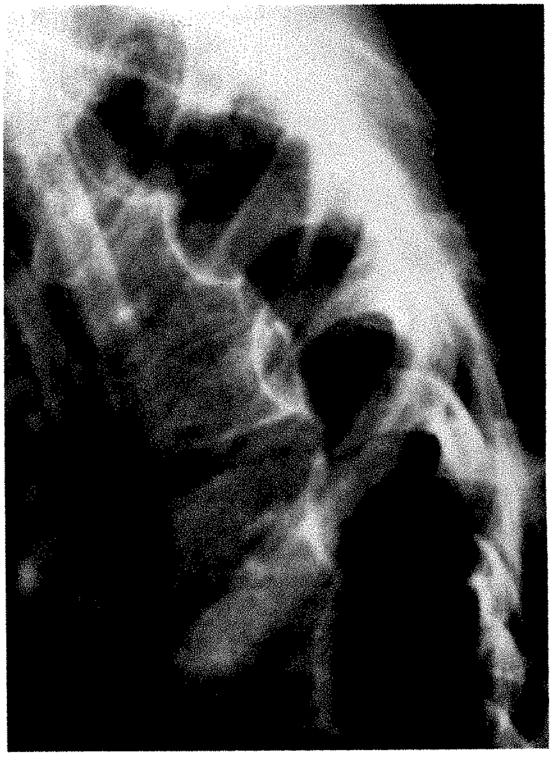

FIG. 3. Case I. With air as contrast agent, the contents of the spinal canal are completely visible. The spinal cord is normal in size and position with respect to the bone abnormalities. No neurofibromas are shown.

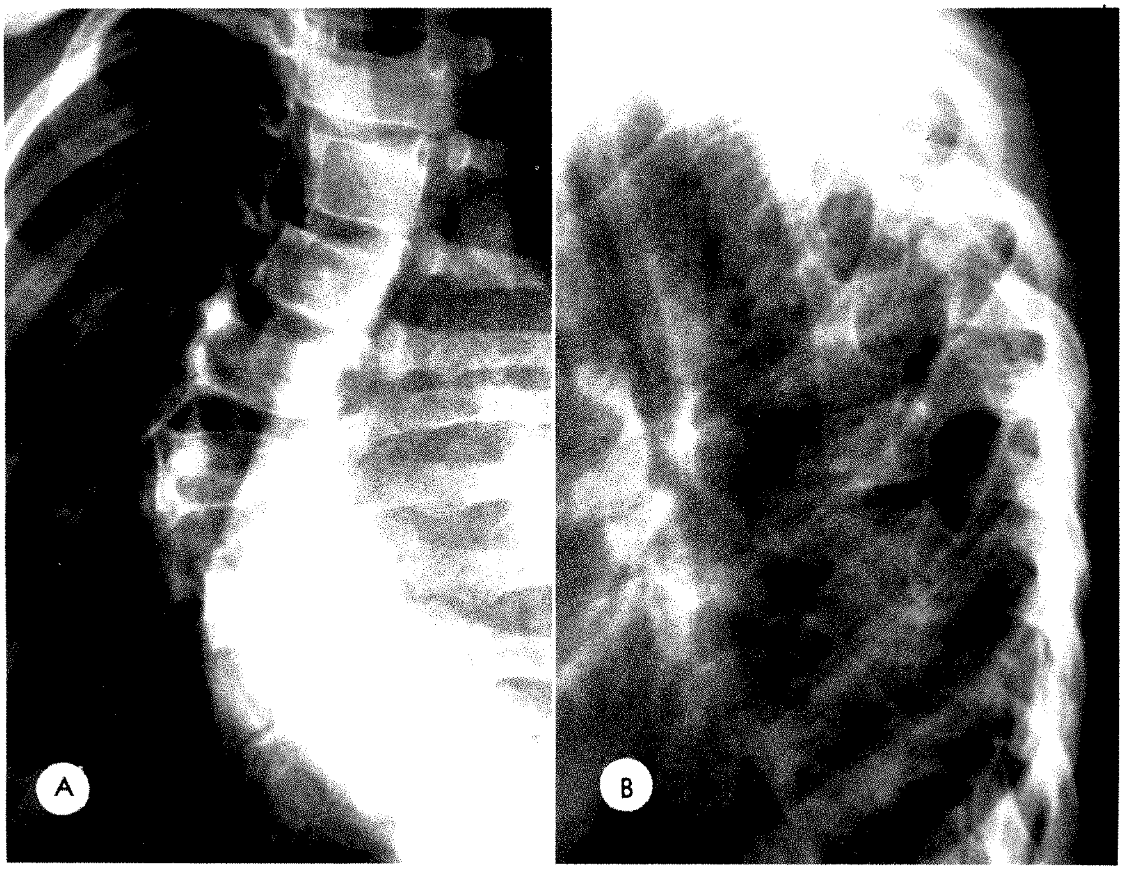

Fig. 1. Case 1. (*A*) Frontal and (*B*) lateral thoracic roentgenograms show abnormal spinal curves. The pedicles of vertebrae beginning at T-3 are misshapen. The spinal canal is also widened at the expense of the vertebral centra which are eroded posteriorly. The vertebral ends of the right fifth and sixth ribs are the most conspicuously deformed.

lateral view showed deep scalloping of the dorsal surfaces of the corresponding centra. The right fifth and sixth ribs showed the characteristic deformity (Fig. 1, *A* and *B*). The conflicting clinical impression of left dorsal scoliosis resulted from an overcompensating secondary curve above the primary one.

A positive contrast myelogram (pantopaque) showed a collection of contrast material at the apex of the scoliotic curve. There were no masses which corresponded to the eroded areas in the vertebrae. The spinal cord was not immersed in contrast material and hence was invisible on this roentgenogram (Fig. 2).

A negative contrast myelogram (pneumomyelogram) at the same spinal levels showed the spinal cord within an expanded but otherwise empty bony spinal canal (Fig. 3).

The patient was admitted to the Neurosurgical Service on February 7, 1960. A preoperative diagnosis of scoliosis secondary to intraspinal meningocele was made and a laminectomy was performed on February 9, 1960. The spinal canal was visualized on the left side at D-6 and D-7. There was a remnant of a spinal motor root at the D-6 level which was very underdeveloped. No sensory root was identified at that level. At D-7 neither a motor nor a sensory root was found. A large spinal fluid filled sac was present around the cord. This pouched into the intervertebral foramina at both visualized levels. The cord was not abnormal in appearance and did not represent failure of fusion. Neurofibroma masses were not present.

The patient was transferred to the Orthopedic Service on February 16, 1960, for treatment of her scoliosis. The curve had advanced from 52° to 60° in 3 months. On February 23, 1960, a spine fusion was done at the levels of

ACQUIRED THORACIC ABNORMALITIES IN NEUROFIBROMATOSIS*

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THE neurofibromatosis of von Recklinghausen is a well known but rare disease. Its most obvious expressions include cutaneous pigmentation (café au lait spots) and soft superficial nodules (fibroma molluscum). In many patients there are associated subcutaneous and deep neurogenic lesions. In addition to these neural and ectodermal changes, there is evidence of localized mesodermal dysplasia involving bone and meninges in some patients. The subarachnoid space may become dilated and herniation of the dura and arachnoid matter into the chest has been described in a number of cases.[4,15] While direct pressure from adjacent neurofibromas undoubtedly explains some of the bone erosion and deformity shown roentgenographically in this disease, this is not an entirely satisfactory explanation for all of the changes in the spinal column. The following cases demonstrate acquired thoracic abnormalities resulting in marked dorsal scoliosis in which bone changes did not result from pressure produced by neurofibromata.

REPORT OF CASES

CASE I. D.T. was first seen at the University Hospital on September 1, 1959 at the age of 8 years and 5 months.

Six weeks previously the mother had noted a curvature of the spine to the left in the thoracic region associated with prominence of the left upper thoracic ribs. She stated that for an unknown period of time the child had poor posture but no spinal curvature had been noted. No symptoms relating to the musculoskeletal system were present. The child had no limitation of activity. She was an average student.

The patient was born after 9 months gestation without prenatal complications. The birth weight was approximately 7 pounds. There were no complications at the time of delivery nor during the routine subsequent hospital stay. In infancy there had been no feeding problems. Toilet training was accomplished at 1 year. The child received routine immunizations with DPT and poliomyelitis shots. Childhood illnesses and operations included removal of tonsils and adenoids, german measles, chickenpox, and approximately two upper respiratory infections per winter. At the age of 1 year, a pigmented area appeared over the midline of the upper dorsal spine. Since then, numerous 1 to 3 cm. areas of hyperpigmentation had developed throughout her body.

The patient's parents were both adopted and no family history was available. Siblings included a sister, aged 13, with a cavernous hemangioma, and sisters, 5 and 11 years of age, who were healthy. There was no recognized family history of tuberculosis, diabetes, mental disease, or arthritis.

Examination disclosed that the patient was a prepuberal female somewhat small for her stated age. She tended to list to the right with a dropped right shoulder and a prominent right hip. There was a large café au lait spot over the posterior chest with several smaller spots elsewhere on the trunk and extremities. No subcutaneous tumors were felt. Clinical examination of the back revealed the left scapula and ribs to be prominent in the dorsal region. No other abnormalities of the musculoskeletal system were noted. Hypalgesia in the distribution of D-6 through D-9 was noted, but this finding was somewhat variable. The deep tendon reflexes were equal and were graded as 1 plus. The plantar reflex was flexor.

Frontal and lateral thoracic roentgenograms showed thoracic kyphoscoliosis of 52° with the convexity of the primary curve to the right. The pedicles of at least 5 vertebrae were misshapened on the frontal projection while the

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age. Without the history of disease, the changes would not have excited special comment.

Somewhat similar defects of ossification in membranous bone may be seen in osteogenesis imperfecta of the tarda form.[4] Wide lambdoid and sagittal sutures are recognized at birth, and multiple wormian bones may persist into adult life.[26] The progressive development of isolated areas of ossification, producing a "mosaic" appearance of wormian bones is also prominent in "familial" idiopathic osteoarthropathy. Hypophosphatasia[7] is associated with wide sutures which may appear several months after birth and may return to normal by 8 to 12 months of age. Craniosynostosis, which commonly occurs subsequently in hypophosphatasia, has not been noted in idiopathic osteoarthropathy. Engelmann's disease (progressive diaphyseal dysplasia[18,23,25]) is characterized by thickening and sclerosis of the cortex of the diaphysis of the tubular bones and frequently the bones of the skull, with abrupt demarcations and loss of normal trabeculation of the involved areas. Widened cranial sutures, elongated extremities, soft tissue changes and neuromuscular signs may be present. The widened sutures and fusiform diaphyseal enlargement are not unlike the findings in our cases, particularly after there has been an accumulation of periosteal new bone as seen in the later stages of active idiopathic osteoarthropathy. Thus, confusion in roentgenologic differentiation of these two entities is obvious, particularly if serial studies are not available. The lack of neuromuscular abnormalities and of amorphous sclerosis of the bones of the skull as seen in Engelmann's disease and the presence of arthropathy, eczema, early periosteal elevation and clubbing should direct one's attention to idiopathic osteoarthropathy.

Other causes of juxta-sutural cranial radiolucencies include cleidocranial dysostosis,[26] intrauterine aminopterin damage,[20] hypothyroidism[27] and hydrocephalus. These syndromes usually can be recognized easily by the various associated stigmata and differentiation from idiopathic osteoarthropathy should not be a problem.

The postnatal development of idiopathic osteoarthropathy in Case I, with resultant progression and subsequent improvement, is similar to, though less pronounced than the evolution of the disease in her siblings and in our Case II. The condition under consideration in its possible response to the presence and subsequent removal of an excitor factor is similar to the secondary form of osteoarthropathy. While the triggering mechanism remains unknown in idiopathic osteoarthropathy, sensitivity to the exciting factor(s) may be extremely high. Information may be provided by long term follow-up studies on individuals with idiopathic osteoarthropathy and their families, but also may be derived from careful retrospective studies of individuals with what appears to be other forms of osteoarthropathy.

SUMMARY

Two case reports of idiopathic osteoarthropathy with cranial defects in infants are presented. The dramatic roentgenographic manifestations associated with this particular form of the syndrome are illustrated. The first infant, with 2 older siblings with the disease, was examined at birth and found normal. The gradual postnatal development of the mild clinical and roentgenographic changes with dramatic improvement by 3 years of age was recorded. The second infant had severe abnormalities by 6 weeks of age and their evolution was followed for 9 years. Differential diagnosis and possible interrelationship with other diseases are discussed. Retrospective evaluation of patients with osteoarthropathy of any form is recommended to determine whether there is evidence of the clinical syndrome of idiopathic osteoarthropathy with cranial defects in infancy, and familial studies are indicated to elucidate the etiology.

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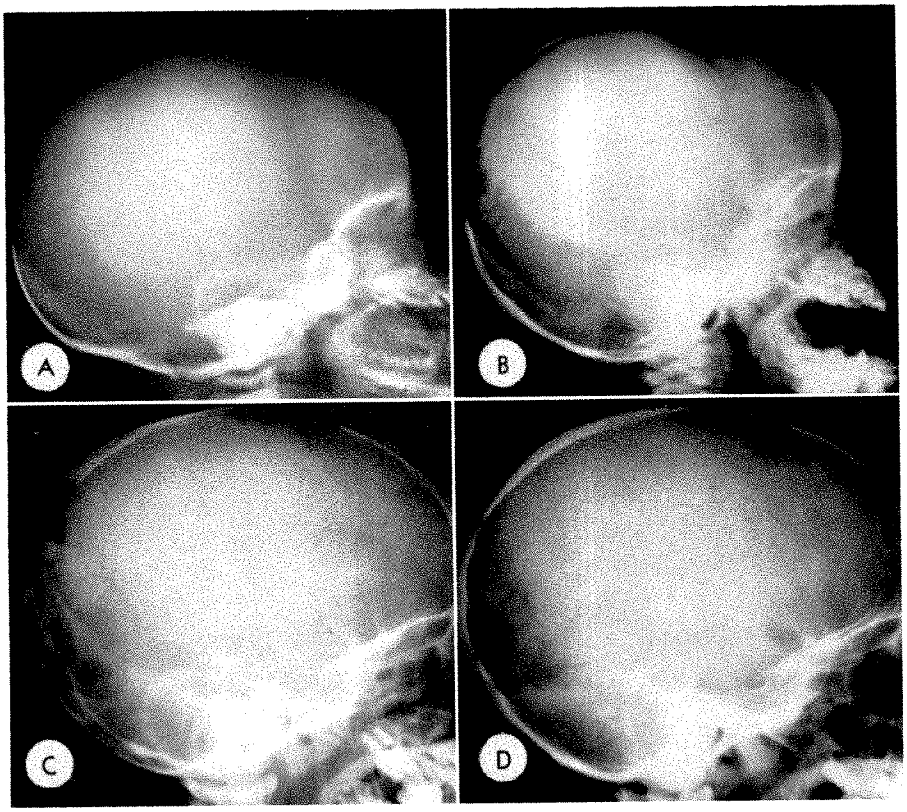

Fig. 6. Case II. Sequence of cranial changes. (*A*) 6 weeks; (*B*) 1 year; (*C*) $4\frac{1}{2}$ years; (*D*) $8\frac{1}{2}$ years. Widened sutures persisted up to 6 years of age, and residual radiolucencies in the region of the lambdoid sutures persisted at 9 years.

patient. Eczema was similarly associated, although no record of any dermatologic manifestations was found in our Case II.

Of extreme interest to us is the normal skull and appendicular skeleton at birth in Case I and the development, some months after birth, of widening of the sagittal and lambdoid sutures with relative sparing of the coronal sutures. The cranial changes are therefore not necessarily congenital as suggested by Currarino *et al.*[8] but can develop postnatally. Clinically, one finds large fontanels but no evidence of actual widening of the sutures by palpation. The wide sutures probably represent a defect in the mechanism of ossification which may appear at or following birth. The triggering mechanism for this latent defect is unknown, but it apparently becomes overshadowed or corrected as evidenced by the reversal toward normal of the roentgenographic abnormalities in all patients. Upon careful re-examination of Currarino and co-workers' patients, we noted that the small radiolucent defects had not disappeared completely even up to 11 years of

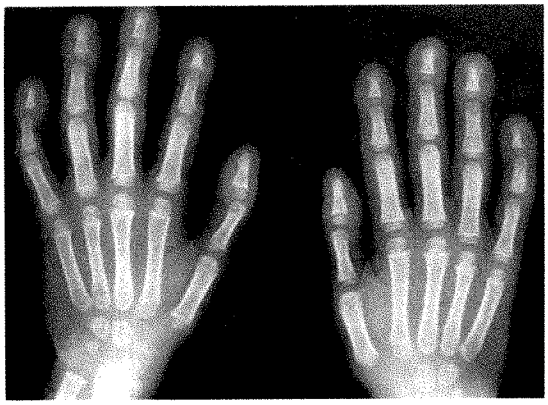

Fig. 7. Case II. Age $4\frac{1}{2}$ years. Clubbing of soft tissues of fingers is clearly shown.

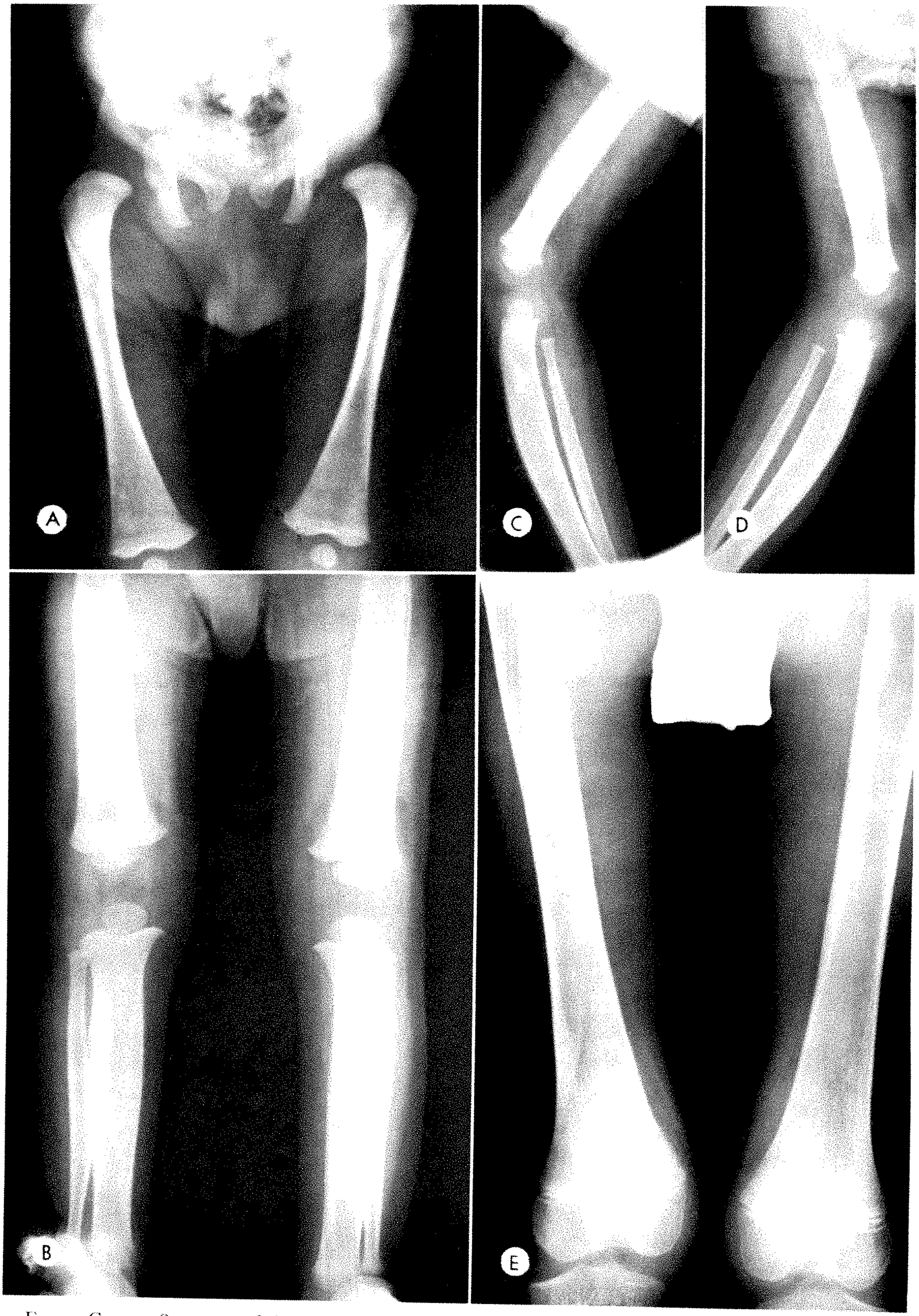

FIG. 5. Case II. Sequence of changes in lower extremities. (*A*) 6 weeks; (*B*) 1 year, frontal projection; (*C* and *D*) 1 year, lateral projection; (*E*) 8½ years.

though definite neurologic abnormalities were not elicited. The body weight of 55 pounds and height of 52 inches were within normal limits. Multiple laboratory studies were obtained and were normal. The child was apparently asymptomatic except for an awkward gait.

DISCUSSION

Idiopathic osteoarthropathy was first described by Friedreich[11] in 1868 and thereafter case reports describing the many variations of the syndrome appeared in the literature. The exact similarity to the secondary form (Marie-Bamberger's "hypertrophic pulmonary osteoarthropathy") has been noted by many authors.[2,6,12,15,18] Mendlowitz,[21] and Vogl and Goldfischer,[30] in comprehensive reviews, attempted to combine the various manifestations into one disease process. Various forms of idiopathic osteoarthropathy are known, such as simple clubbing,[24,28,31] clubbing and periosteal new bone formation with or without arthropathy[5,9] and pachydermoperiostosis with associated thickened skin, particularly of the face.[1,2,29,30] Suggested etiologies are many[2,13,16,22,29] and reproduction of the entity by vagotomy[15] and by production of arteriovenous fistulas[22] is reported. Baldwin[2] suggests that approximately 25 per cent of the cases may have a recessive or incompletely dominant gene responsible. Theoretically, the multiple manifestations of this disease may be comparable to genetic abnormalities which, upon proper stimulation, display one or many manifestations of the syndrome. In order to leave open the question of etiology, we have avoided the term "familial" as originally employed by Currarino and his associates.[8] The mother of the 3 children with the disease occasionally complained of mild joint pain during cold and humid weather,[8] although roentgenograms were normal. However, family history is lacking in our Case II, and until better information is available on parents and other relations of children with the disease, conclusions cannot be drawn.

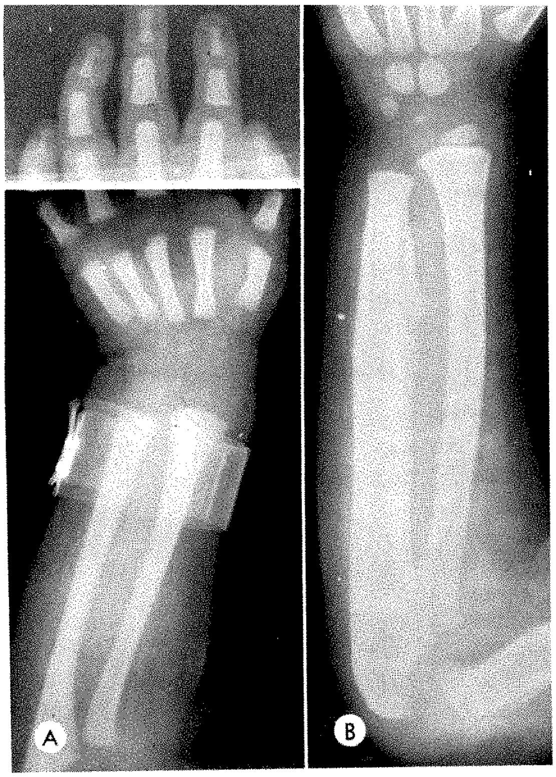

Fig. 3. Case I. Sequence of changes in arm. (*A*) Newborn; (*B*) 2 years.

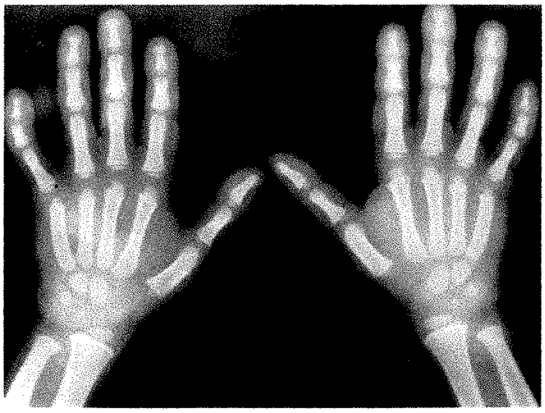

Fig. 4. Case I. Mild soft tissue clubbing of fingers at 2½ years of age.

The 4 children described or alluded to in this report all possessed similar roentgenographic and clinical findings. Soft tissue clubbing and periosteal elevation were quite prominent by the second year of life. Arthropathy consisting of pain, swelling, and joint effusion was usually associated with the recurrences of periosteal elevation, and persisted to adolescence in the oldest

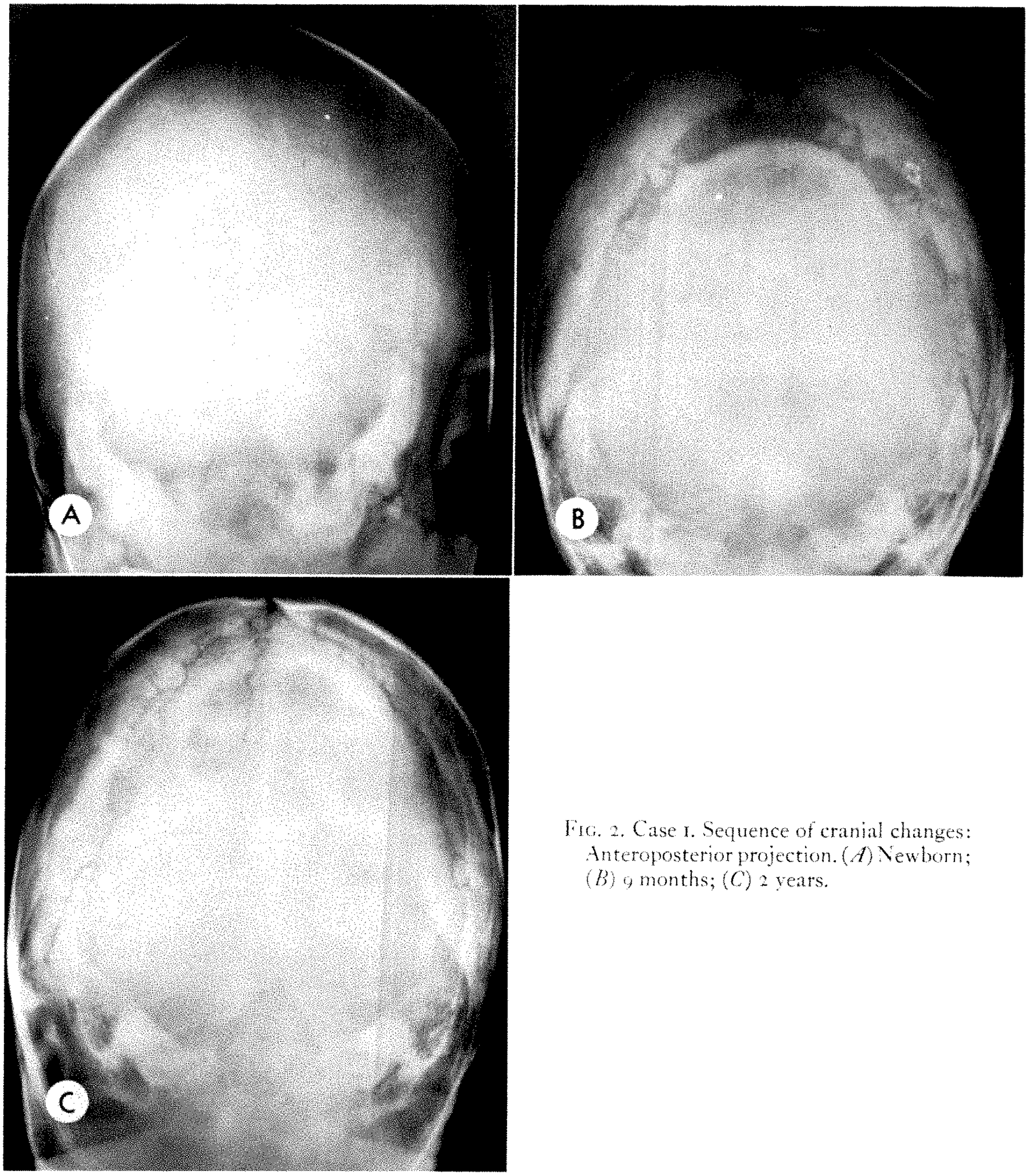

FIG. 2. Case 1. Sequence of cranial changes: Anteroposterior projection. (*A*) Newborn; (*B*) 9 months; (*C*) 2 years.

When the periosteal elevation began to decrease in amount, the diameter of the shaft decreased, and by 9 years only a clumsy or bulky appearance to the diaphyseal portions of the long bones was recognized. Serial roentgenograms of the cranium demonstrated slow but progressive ossification of the membranous bones (Fig. 6, *A–D*). At 9 years of age, the skull was normal except for several residual radiolucencies in the lambdoid sutures. The fingers were long and slender but the soft tissues of the terminal phalanges were clubbed (Fig. 7). The bone age was below normal according to the standards of Greulich and Pyle.[14] The chest roentgenogram was normal. Clubbing and joint swelling with flexion contractures were unchanged in comparison with previous examinations. There was no mention of eczema or other dermatologic abnormalities in the available history. Mental retardation was suspected al-

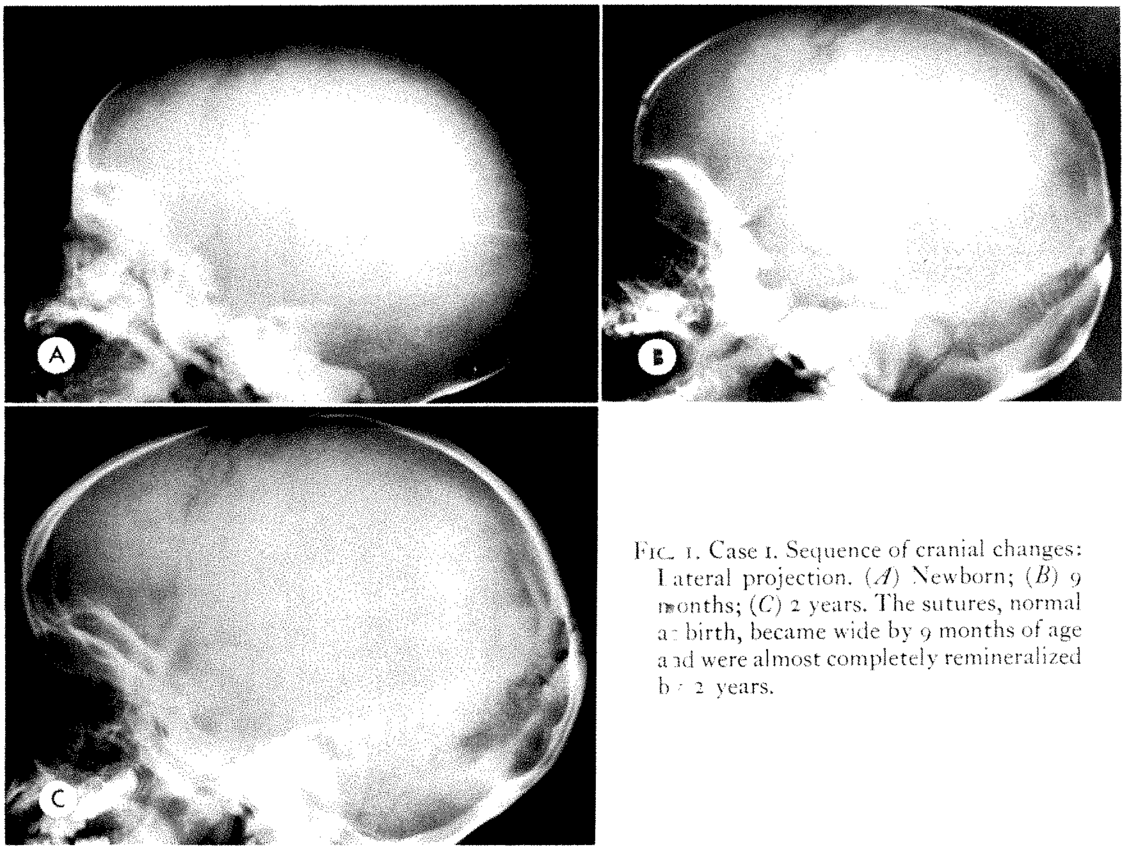

FIG. 1. Case I. Sequence of cranial changes: Lateral projection. (*A*) Newborn; (*B*) 9 months; (*C*) 2 years. The sutures, normal at birth, became wide by 9 months of age and were almost completely remineralized by 2 years.

was asymptomatic. Laboratory studies were again normal. Serum potassium of 6.4 mEq./L. was recorded but its accuracy was doubted.

Roentgenograms of the skull at 2 years of age (Fig. 1*C* and 2*C*) demonstrated normal size and shape with several small radiolucencies in the lambdoid sutures bilaterally. The fontanels were closed. Moderate bilateral periosteal elevation of the ulna (Fig. 3*B*), tibia and fibula, and soft tissue clubbing of the fingers were identified roentgenographically (Fig. 4). At the age of 2½ years, the periosteal elevation was only faintly present and there was mild residual diaphyseal enlargement. Recurrent eczema over the back and shoulders and occasional pain and swelling of the knee joints were present at 3 years of age.

CASE II. This 9 year old Negro male, E. G., was born to a 15 year old mother who had had pertussis during the second trimester of pregnancy. History concerning antecedents or collaterals is not available. The birth, on April 15, 1954, was uncomplicated and the child appeared normal. Serologic test for syphilis on the cord blood was negative. At 6 weeks of age, the child was admitted to the Children's Medical Center, Dallas, Texas, because of malnutrition. Skull roentgenograms demonstrated wide sagittal, lambdoid and squamosal sutures. The child regained weight rapidly but was returned to the hospital at 9 months of age with iron deficiency anemia, recurrence of malnutrition, growth retardation and an inability to extend the legs at the knees. The blood urea nitrogen, VDRL test, serum proteins and calcium were normal.

Roentgenograms of the long bones at 9 months of age demonstrated periosteal elevation, genu valgum, anterior tibial bowing and joint effusion bilaterally. Semi-annual or annual roentgenograms were obtained over the next 9 years (Fig. 5, *A–E*). By 1½ years of age, the midshaft diameter of the tubular bones had markedly increased in size and resembled the diaphyseal enlargement in Engelmann's disease. The onion peel appearance of recurrent periosteal elevation and new bone formation producing the midshaft enlargement was present during the second through the fourth year.

opposition of surface tension within the small air chambers of the lung. The force of surface tension increases as the diameter of a structure decreases. There is experimental indication of the presence of such a substance. The deficiency of this substance was demonstrated in lungs of patients with hyaline membrane disease. According to this theory, there would be no effect of this substance until after the creation of an air-liquid interface. This would occur after the first breath. Thereafter the normal lung would have normally low surface tension and the lung with hyaline membrane disease, lacking surface active material, would have high tension, encouraging collapse of alveoli on expiration.

SUMMARY

The clinical, pathologic and roentgen features, as well as the theories of pathogenesis, of hyaline membrane disease are discussed. The roentgenographic findings of 6 proven cases were reviewed.

Consistent roentgen features of hyaline membrane disease are finely granular, reticular areas of increased density in the lungs, and air bronchogram far into periphery of lung. Frequent findings are peripheral areas of radiolucency and confluent areas of consolidation in the lungs. The confluent areas of consolidation are considered to be late findings.

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OBSTRUCTING TRACHEAL HEMANGIOMA IN INFANCY*

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HEMANGIOMAS of the trachea in infants causing airway obstruction are rare. Since the obstructions may be severe or even fatal, a high index of suspicion is needed. The purpose of this paper is to review the features of this condition and to present the findings in a recent patient.

REPORT OF A CASE

D.N., a 3 month old Negro male, developed gasping respirations and cyanosis without cough, coryza, or fever at the age of 3 weeks. The patient was treated symptomatically at another institution and did well for short periods of time. The respiratory difficulty increased and stridor and sternal retractions developed. The infant improved slightly by the use of a vaporizer.

The patient was a product of an uncomplicated gestation period and delivery. Growth and development were normal. At the age of 2 weeks urticarial lesions appeared on the face but subsided spontaneously. A right inguinal herniorrhaphy was tolerated at the age of 1 month.

On physical examination the infant was found to be in mild respiratory distress with inspiratory stridor that increased with crying. Cyanosis was present with vigorous crying. No dermal hemangiomas were found.

Indirect larnygoscopy was negative. Multiple roentgenograms of the trachea and larynx were obtained during fluoroscopy. These showed in the proximal trachea a 1 cm. area of narrowing (Fig. 1, *A* and *B*). The mass was primarily on the posterior wall of the trachea and narrowed the lumen by more than 50 per cent. The aryepiglottic folds, vallecula, and laryngeal ventricle appeared normal. Posteroanterior and lateral roentgenograms of the chest and barium examination of the esophagus were normal.

Under general anesthesia a Flagg laryngoscope was passed through the vocal cords. Below the cricoid cartilage a soft mass, described as 5 mm. in diameter, was observed which narrowed the trachea to 2 mm. in diameter. It was elected not to biopsy the lesion, because any trauma could necessitate a tracheostomy. The diagnosis was thought to be a chondroma. The plan was to follow the patient in the outpatient department, hoping that the trachea would grow faster than the mass and the relative respiratory obstruction would become less.

The patient was discharged from the hospital but became progressively worse over the next 3 weeks with wheezing and coughing greatest at night. At the age of 4 months surgical intervention was deemed necessary and the trachea was opened widely ventrally from the first through the fourth tracheal ring. A 3×2 mm. submucosal hemangioma was found. The posterior tracheal wall mucosa was opened vertically and the mass dissected out as much as possible. The mass was smaller at the time of surgery than it was on the preoperative roentgenogram. A polyethylene stent was put in place and a tracheostomy tube was inserted. The microscopic diagnosis on the removed tissue was hemangioma, capillary type.

Roentgenograms of the airway 2 months postoperatively showed interval disappearance of the mass projecting into the trachea. The site of the tracheal incision anteriorly demonstrated some invagination on inspiration. The patient otherwise was doing well, although he was able to tolerate extubation for only short periods of time.

DISCUSSION

Hemangiomas of the trachea in infancy usually are located in the subglottic region. They are to be differentiated from the more common cordal or supraglottic hemangiomas of the adult.[7] Nineteen cases were reported through 1958 by Campbell *et al.*[3] Since that time a total of 65 patients have been reported.[1,2,4,5,8,9,11,13,14,15,16,18,20] Because hemangiomas may collapse after death and not be diagnosed unless specifically looked for, the condition may be more common than suspected. Doermann *et al.*[5] recommends that careful sectioning of the subglottic area be performed in all cases of sudden death in infancy.

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The symptoms are those of respiratory tract obstruction of varying degrees of severity. Inspiratory stridor is the earliest and most constant symptom. The stridor may become biphasic and be associated with suprasternal or sternal retraction. Dyspnea and wheezing are also common. Cyanosis and cough may be present. The voice and cry usually are clear. Hemoptysis is rare. The most important clinical feature of this condition is the episodic nature of the obstruction. Periods of relative well being may alternate with severe respiratory distress. Noisy respirations or wheezing may precede or follow a severe obstructive episode. The recurrent nature of the symptoms is due either to superimposed inflammatory disease or variation in the size of the tumor depending on its blood content.[2,6] Although more than 90 per cent of the infants develop respiratory distress prior to the age of 6 months, the clinical symptoms do not usually start at birth. Commonly, there is a period of several weeks or months prior to the onset of symptoms, which may develop insidiously or suddenly. Females are affected more frequently than males in a 2 to 1 ratio.[14] Approximately one-half of the reported cases have had hemangiomas elsewhere.[14] Therefore, stridor which is characteristically episodic in infants less than 6 months of age, if associated with hemangiomas in other parts of the body, should suggest the possibility of a tracheal hemangioma. Infantile hemangiomas usually are interpreted as hamartomatous malformations rather than true neoplasms.[19] Histologically, the hemangiomas are usually of the cavernous rather than capillary type, but either may be present.[6] A predominant endothelial component can produce a more solid type of tumor.

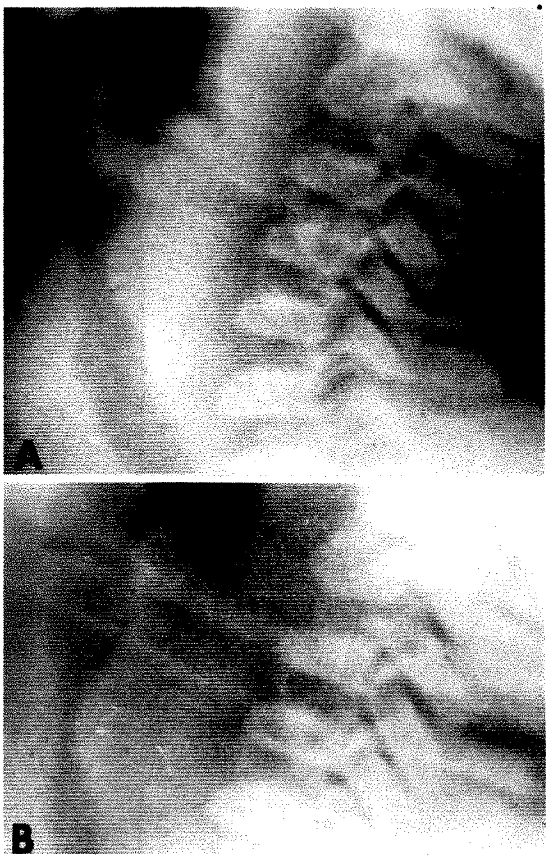

Fig. 1. (*A* and *B*) Roentgenograms of the neck showing a mass projecting into the proximal trachea.

Roentgenograms of the airway showing narrowing of the proximal trachea can lead to a presumptive diagnosis of hemangioma which then can be confirmed by direct inspection. Information also will be obtained about the extent and size of the tumor. Contrast studies of the airway to define better the extent of the hemangioma could facilitate the establishment of portals for radiation therapy or could facilitate surgical planning. Roentgenograms of the chest and contrast studies of the esophagus are invaluable in excluding other causes of respiratory obstruction and distress.

Endoscopy is the usual way the diagnosis is established. The tumor projects into the airway most frequently below the cords. It is a sessile mass and has a distinctive reddish-blue color varying somewhat with the degree of vascular patency and depth beneath the mucosa. The tumor usually is compressible and is located on one wall of the trachea. It may be circumferential, however. The endoscopic and gross appearance, the location, and the clinical picture are sufficiently diagnostic to institute therapy without histologic confirmation.[6] Biopsy is stated to be hazardous and usually unnecessary, but should be resorted to in patients with lesions differing from the characteristic picture.[14] There is less of a risk of hemorrhage in a firm noncompressible tumor. Any localized sessile bulging in the subglottic area in infancy should be suspected of being a hemangioma. The nature of the lesion may not be appreciated by laryngoscopy as in our patient in whom the postlaryngoscopy diagnosis was chondroma. Pierce[16] recommended direct visualization of the lesion which should diminish greatly or disappear completely after the patient receives 2 minims of subcutaneous epinephrine.

The differential diagnosis would include laryngotracheobronchitis, chondromalacia of the epiglottis, larynx, or trachea, vascular ring, tracheal web or stenosis, cord paralysis associated with birth trauma, H-fistula, mediastinal tumors, and other laryngeal tumors—notably papillomas, chondromas, and mucous retention cysts of the larynx. The recurrent nature of the symptoms, the infant's age of less than 6 months, hemangiomas elsewhere, the lack of fever or leukocytosis, along with the roentgenograms showing the lesion and its localization should lead to a presumptive diagnosis.

Tracheal hemangiomas have been treated successfully by irradiation, surgical excision and cautery. Entubation or tracheostomy can relieve the acute obstruction when the hemangioma is in the usual subglottic position.

Irradiation is stated by most authors to be the treatment of choice.[2,4,6,7,9,12,14] Small amounts of radiation either with or without preliminary tracheostomy are recommended. Ferguson and Flake[6] successfully treated 16 of 17 patients with orthovoltage therapy of 250–300 r in a single dose with opposing or oblique portals of 2–4 cm. Smaller lesions were treated without tracheostomy and larger lesions with tracheostomy. A slightly higher dosage with fractionation over a 4–6 day period was used in intermediate size lesions without tracheostomy. In general, the dosage recommended in the literature ranged between 1,200–1,500 r fractionated over a 3 week period.[12] A definite and adequate response to irradiation 6–8 weeks after therapy was reported in 16 of 17 lesions reported by Ferguson and Flake[6] using a total dose of 500 r or less.

The increased incidence of carcinoma of the thyroid in patients receiving irradiation in this area[17] has caused some authors to state that complete excision of the tumor is the preferred therapy.[20] It is agreed that untreated lesions may be fatal. Surgical treatment has not met with conspicuous success, however. Postoperative stenosis is a difficult therapeutic problem, if it occurs. Our patient developed inspiratory retraction of the trachea at the surgical site. Hemorrhage may also occur. Decanalization after any mode of therapy may be difficult as it is with infants receiving a tracheostomy for any reason. Campbell *et al.*[3] have emphasized the danger of tracheostomy alone not followed by obliteration of the hemangioma. Seven patients treated in this manner died.

There are examples of spontaneous regression of tracheal hemangiomas after the age of 6 months.[10] Since cutaneous hemangiomas regress approximately 80 per cent of the time, this observation is not surprising.

SUMMARY

A patient with tracheal hemangioma causing respiratory distress is reported and the features of the condition are reviewed.

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THE ROENTGENOGRAPHIC DIAGNOSIS OF HIRSCHSPRUNG'S DISEASE IN INFANCY*

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AGANGLIONOSIS, or Hirschsprung's disease, has clinical and roentgenographic characteristics presenting in the first days and weeks of life that allow its diagnosis to be made long before actual "megacolon" develops. Since the disease is often a lethal one in infancy,[3,5,6,8] with high mortality from enterocolitis, early diagnosis is essential.

Following Hirschsprung's 1887 report on "sluggishness of stool in the newborn,"[12] scattered clinical and pathologic reports of the same disease appeared. Pathologists from Tittel[21] in 1901 to Whitehouse and Kernohan[22] in 1948 noted ganglion cell absence in the normal appearing distal sigmoid and rectum. These findings were not clinically appreciated until Tiffin, Chandler and Faber[20] attempted to relate the disordered motility and constipation in an infant to the aganglionosis found at postmortem examination in the rectosigmoid colon.

In 1945, Ehrenpreis,[9] a major contributor to the understanding of the neonatal manifestations of Hirschsprung's disease, showed clearly that infants dying of enterocolitis following weeks or months of distention and constipation had the same disease as the older constipated children with frank megacolon.

It remained for Hiatt[11] and Swenson *et al.*[19] to devise physiologically sound operative measures. They removed the nonperistaltic segment and anastomosed the normal bowel to the anorectum by means of a "pullthrough" procedure. They demonstrated by motility studies the abnormal tone and spasm in the aganglionic segment that obstructed the normal bowel and eventually produced the hypertrophied dilated "megacolon."

Despite this accumulation of clinical, pathologic and surgical data,[9,11,19,25] the disease remains a major problem in diagnosis to clinicians, radiologists and surgeons alike. The average patient is still not diagnosed until in later infancy, although many may have been studied roentgenographically in the newborn period and some may have even undergone exploratory laparotomy with the diagnosis being missed.

We have reviewed our roentgenographic experience with aganglionosis since 1948. Only patients with both microscopic proof of aganglionosis and available roentgen studies were included in this report. Lack of roentgenograms eliminated more than 50 patients who had early pull-through procedures; this group included many older children.

Seventy-six patients were studied; there were 56 males and 20 females, reflecting the male predominance. Five patients had involvement of the entire colon and terminal ileum; 3 had ascending colon or hepatic flexure levels of transition; 5 showed transverse or splenic flexure colonic transitions; and 63 patients presented with the more typical mid or lower sigmoid transition levels. Terminal rectal transition with "megarectum" was not found. All patients had aganglionosis from the zone of transition distally to the distal rectum; skip areas of involvement were not found.[2,4,16]

CLINICAL FEATURES

The infants are initially well, but by 36 to 48 hours they become distended, some markedly, some slightly.[2,4,6,8,10,13,14] Bile tinged emesis is common. Meconium passage, accomplished by 90 per cent of normal infants in 24 hours,[9,17] is delayed, sometimes with spontaneous relief but more often initiated by digital or thermometer manipulation of the rectum. This is the initial "decompensation" period; it does not appear to be correlated with the length of the aganglionic involvement.[4,16] If the infant "compensates," he may seem well, and may be discharged only to have recurrent distention, constipation, and emesis in the following weeks or months. Usually, 9 to 12 months will elapse before gross megacolon is found.

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Associated congenital anomalies have not been noted. Urinary tract obstruction and infection have been conspicuously absent. A small number of patients have had affected siblings and several patients have had Down's syndrome (trisomy 21 or mongolism).

It is this first period of clinical "decompensation" that should lead to clinical suspicion and roentgenographic studies. The diagnosis can be made promptly and with accuracy.[2,10,14,15,16]

Failure to diagnose the disease can lead to two results. The first is that of lost time, with obvious megacolon following chronic constipation presenting in a year or so. The second is the chance, as high as 50 per cent,[3,5,6,8,16] of the infant developing enterocolitis; death from one or repeated attacks of such a complication occurs in 25 to 50 per cent of affected infants.

ROENTGEN FINDINGS

PLAIN FILM STUDIES

Supine and erect frontal and recumbent lateral roentgenograms may strikingly parallel the clinical findings. The distended infant may show multiple gas-filled loops with air fluid levels (Fig. 1, *A* and *B*) and differentiation of large and small bowel may be extremely difficult. Lateral roentgenograms can be helpful (Fig. 1*C*) in showing the long sweep of the descending colon in the prevertebral area. Five patients have shown extraluminal air paralleling the bowel wall (Fig. 1*C;* and 6, *A* and *B*). Although aganglionosis was proven, mucosal destruction was not present. It appears that distention alone can produce this pattern, though it is more commonly seen in the premature infant with necrotizing enterocolitis without aganglionosis.[23]

The plain roentgenograms may strongly suggest the diagnosis and the gaseous distention may have been relieved by the time the roentgenographic studies are completed. A barium enema examination, however, is needed to separate the large from the small bowel distention and to provide proof of the diagnosis. Such studies should be done on infants with delayed meconium and stool passage, distention and bile emesis even if digital examination seems to relieve the patient.

BARIUM ENEMA STUDIES

Contrast studies, preferably with barium, are carried out with the use of a soft catheter taped to the buttocks. Inflatable rectal balloons should not be used since they distend and obscure the anatomy of the rectosigmoid colon. They may also lead to perforation of the thin-walled infant colon and cause fecal-barium peritonitis (Fig. 2, *A* and *B*). The colon is filled unless a gross caliber change is seen. In the latter event, only several inches proximal to the change are filled in order to avoid obscuration (Fig. 3*A*). Frontal and lateral spot roentgenograms are obtained. No attempt is made to promote evacuation and delayed roentgenograms at 24 hours and, occasionally, at 40 and 72 hours are taken. The lateral view appears to be the most helpful (Fig. 3, *B* and *C*).

The patient with aganglionosis shows the same difficulty in evacuating barium that he has with meconium and stool. This leads to stasis[2,4,9,13,16] which is manifest by persistent distention with colon air-fluid levels and retained contrast material on delayed roentgenograms (Fig. 4, *A*, *B* and *C*). Ehrenpreis[9] was the first to report the abnormal stasis on delayed abdominal roentgenograms in aganglionosis in a comparison with normal infants. The stasis is colonic although small bowel dilatation may be present as well. It is this finding

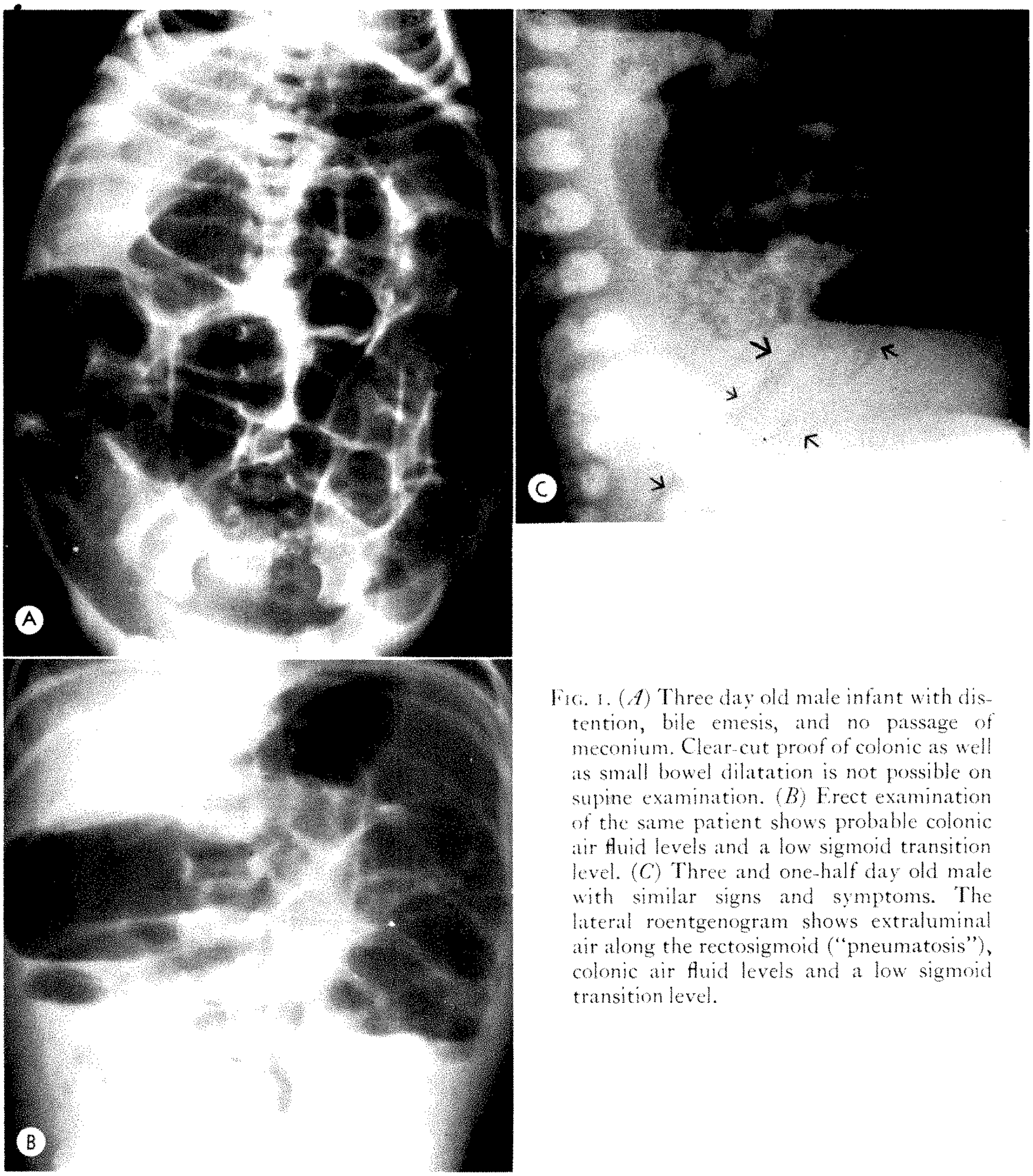

Fig. 1. (*A*) Three day old male infant with distention, bile emesis, and no passage of meconium. Clear-cut proof of colonic as well as small bowel dilatation is not possible on supine examination. (*B*) Erect examination of the same patient shows probable colonic air fluid levels and a low sigmoid transition level. (*C*) Three and one-half day old male with similar signs and symptoms. The lateral roentgenogram shows extraluminal air along the rectosigmoid ("pneumatosis"), colonic air fluid levels and a low sigmoid transition level.

(rather than a morphologic alteration in colon diameter at a transition point with megacolon proximally) that is the most definitive sign of aganglionosis in the newborn.[2,8,11,13,14,15,16,19]

THE TRANSITION SEGMENT

The roentgen transition was noted by Neuhauser[19] as a change in caliber, usually in the lower sigmoid or upper rectum, seen by careful observation during fluoroscopy; the older patients so studied had massively dilated sigmoid colons that obscured the narrow rectum unless skillful positioning was used. Infants in the newborn period lack a fixed megacolon and the transition is less well defined though usually present.[2,9,16] We look for such caliber change but do not stress it.

The roentgen transition frequently does

not correspond to the surgical transition found at the time of laparotomy. Preoperative cleansing enemas, general anesthesia and "spontaneous compensation" may produce an appearance of the colon which may seem normal to the surgeon.

Finally, as noted by Bodian *et al.*[4] transition zones seen roentgenographically and those seen at surgery may differ widely from the true pathologic transition seen on microscopic study. Peristalsis and fecal masses can dilate the proximal aganglionic bowel as well as the normal ganglionic segments.[4,16] Apparent sigmoid levels of caliber transition have been found to be due to splenic flexure transition microscopically (Fig. 5*A*); and apparent distal transverse colon transition, also noted at surgery, was seen with microscopic transition just above the ileocecal valve (Fig. 5*B*). In a $3\frac{1}{2}$ year old girl with repeated sigmoid fecal impactions and a normal barium enema study, transition was noted just above the ileocecal valve.

The diagnosis of aganglionosis can be made without roentgen demonstration of a transition segment in the neonatal period on finding evidence of stasis (colonic or low small bowel in total colonic involvement)[1,2,9,16] associated with the clinical pattern described above.

ILLUSTRATIVE CASE

CASE I. A 3 day old girl was transferred to Babies Hospital with a diagnosis of "sepsis," with jaundice, bile emesis, and abdominal distention. A small meconium stool was passed at 36 hours of age. Plain roentgenograms showed mild small bowel and possible colonic distention with extraluminal air paralleling the left colon (Fig. 6, *A* and *B*). A clinical and roentgen diagnosis of probable sepsis with enterocolitis

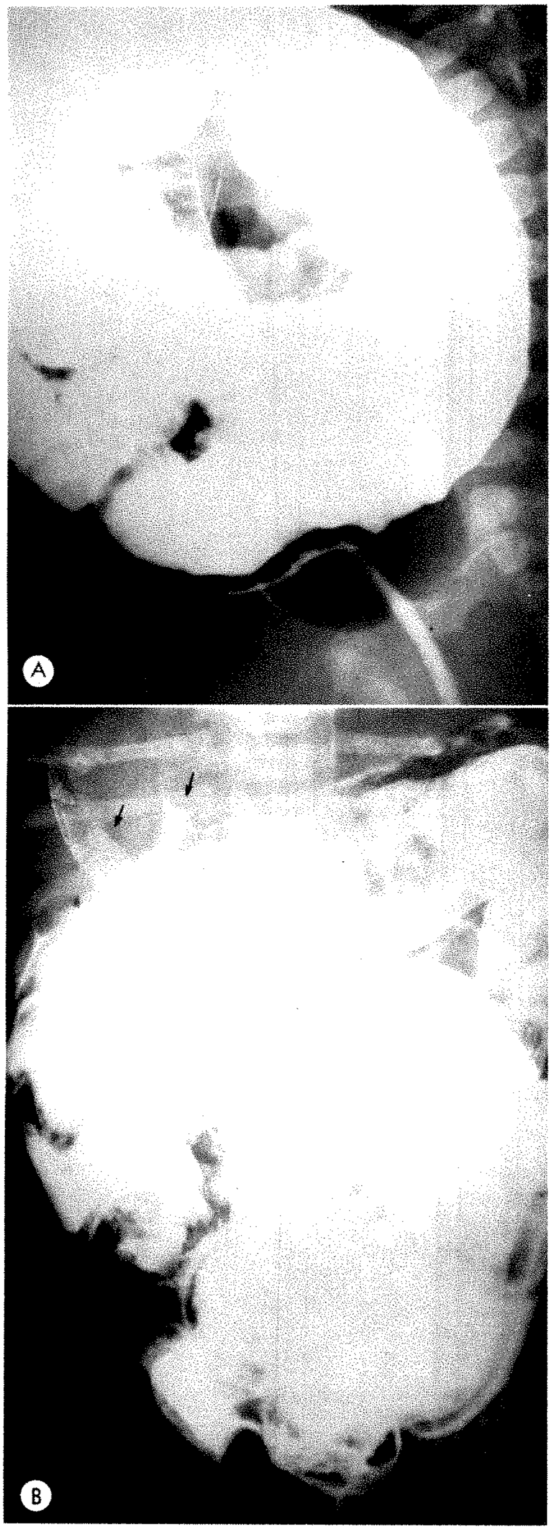

FIG. 2. (*A*) Three day old male showing obstructive signs. A large rectal balloon distends the rectum; extramural barium is present. (*B*) Same patient. Barium outlines the falciform ligament. The patient went into shock several hours after the enema and died. The transition level was found to be the low sigmoid. There was a tear in the sigmoid with barium-fecal peritonitis.

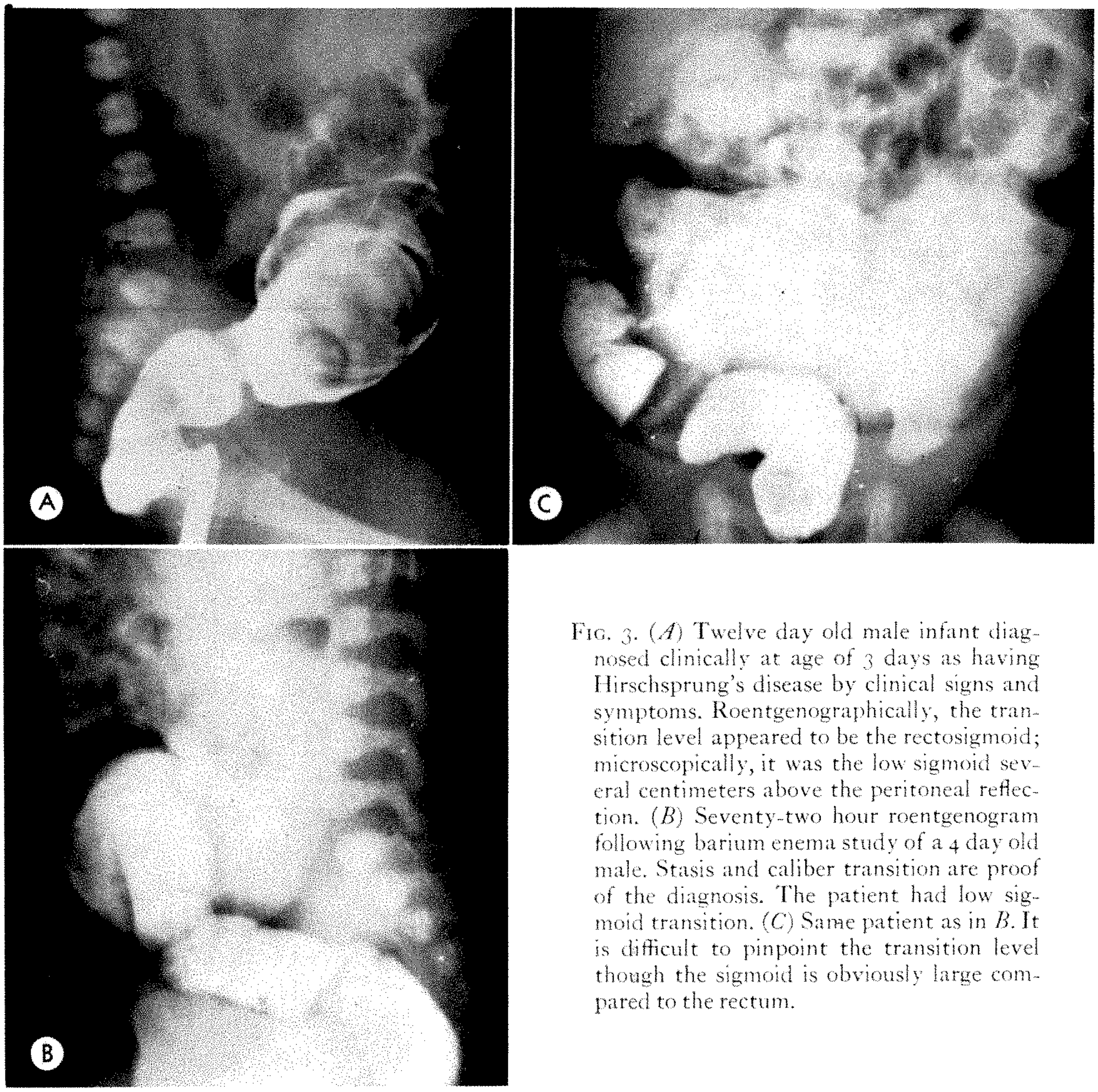

Fig. 3. (*A*) Twelve day old male infant diagnosed clinically at age of 3 days as having Hirschsprung's disease by clinical signs and symptoms. Roentgenographically, the transition level appeared to be the rectosigmoid; microscopically, it was the low sigmoid several centimeters above the peritoneal reflection. (*B*) Seventy-two hour roentgenogram following barium enema study of a 4 day old male. Stasis and caliber transition are proof of the diagnosis. The patient had low sigmoid transition. (*C*) Same patient as in *B*. It is difficult to pinpoint the transition level though the sigmoid is obviously large compared to the rectum.

was made; barium enema study was omitted. Eight cubic centimeters of bile-tinged fluid were aspirated from the stomach. Laparotomy was performed in the hope of finding a correctable abscess or loops of gangrenous bowel; however, no abnormalities were found. Biopsy was not taken.

Five days postoperatively, distention recurred. Hypaque enema studies (Fig. 6, *C* and *D*) showed a grossly normal colon diameter; no transition segment was felt to be present. Nothing had been evacuated per rectum. Massive small bowel reflux of contrast material occurred and 24 hour roentgenogram (Fig. 6*E*) showed colon air fluid levels with stasis. Aganglionosis was diagnosed although the level was undetermined. The jaundice which was related to a transient hemolysis associated with pyknocytotic red blood cells had cleared. All cultures were negative.

After 2 weeks of observation, the infant became hypoproteinemic, edematous, and distended. Repeat plain roentgenogram (Fig. 6*F*) showed huge fecal masses in the large transverse colon. The extraluminal air was gone. A repeat enema study with barium (Fig. 6, *G* and *H*) showed a clear roentgen transition in the splenic flexure. Laparotomy confirmed the gross level; however, frozen section biopsy had to be carried to the proximal transverse colon

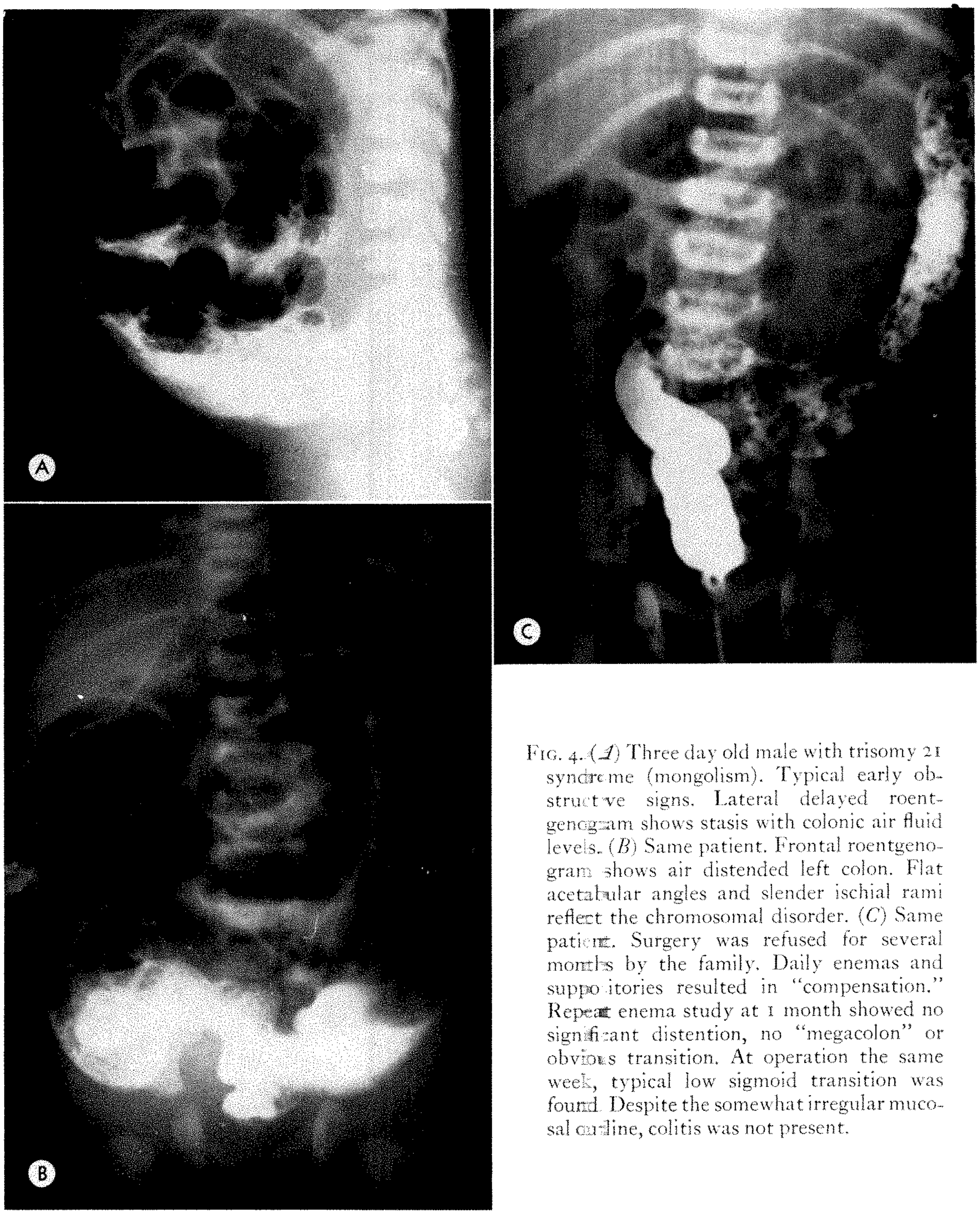

FIG. 4. (*A*) Three day old male with trisomy 21 syndrome (mongolism). Typical early obstructive signs. Lateral delayed roentgenogram shows stasis with colonic air fluid levels. (*B*) Same patient. Frontal roentgenogram shows air distended left colon. Flat acetabular angles and slender ischial rami reflect the chromosomal disorder. (*C*) Same patient. Surgery was refused for several months by the family. Daily enemas and suppositories resulted in "compensation." Repeat enema study at 1 month showed no significant distention, no "megacolon" or obvious transition. At operation the same week, typical low sigmoid transition was found. Despite the somewhat irregular mucosal outline, colitis was not present.

before ganglion cells were found. Colostomy at the hepatic flexure was performed, followed by a pullthrough procedure when the patient was 1 year of age.

Comment. In retrospect, the signs and symptoms followed by a "negative laparotomy" were classic for neonatal Hirschsprung's disease. Most important was the finding of the altered physiologic peristaltic pattern in the absence of a transition

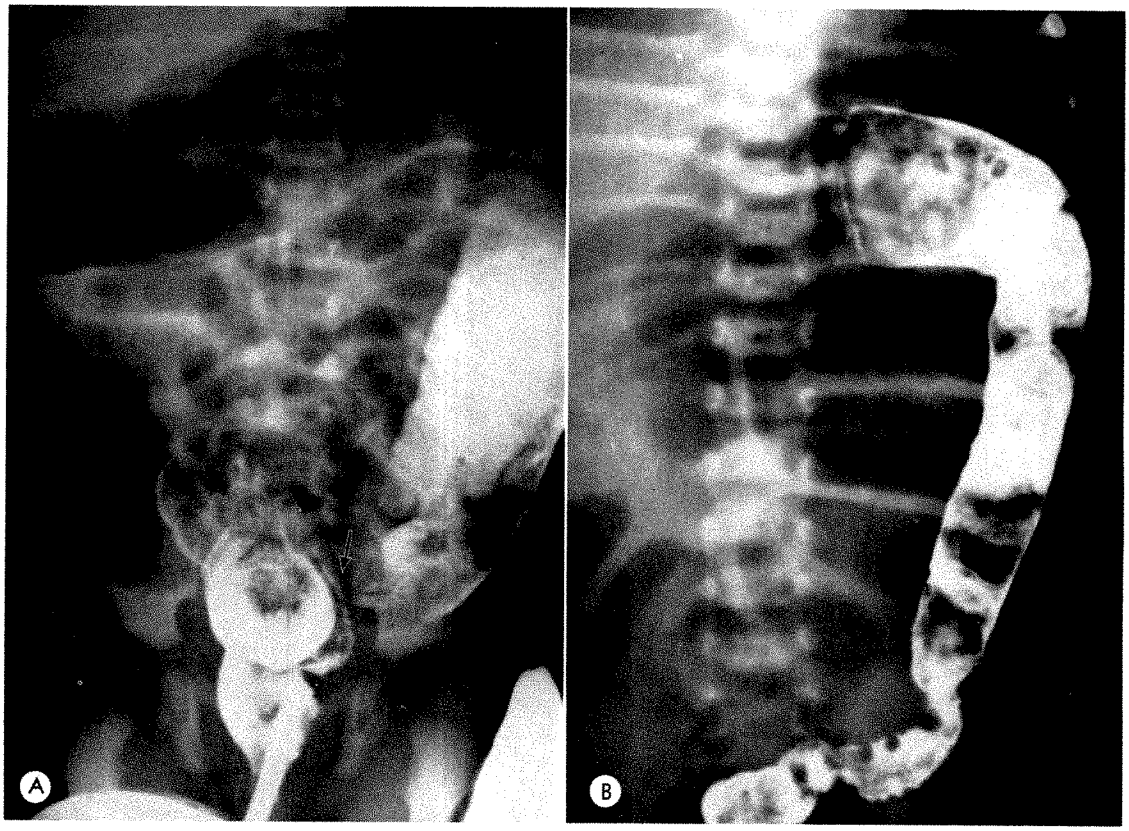

FIG. 5. (*A*) Four day old girl. Roentgenogram shows gross transition in low sigmoid level (arrow) with early decompensation. Spontaneous compensation delayed surgery until the patient was 18 months of age when gross megacolon was present. At operation, ganglion cell transition just below the splenic flexure was found. (*B*) Three day old male whose sibling also had sigmoid transition. Barium enema study shows fecal masses in transverse colon with gross transition. Roentgenograms at 36 and 48 hours showed stasis. Microscopic transition was found just above the ileocecal valve. Surgical transition was at the splenic flexure.

segment. When the "transition" appeared, it was in an area that was aganglionic; a colostomy done here without frozen section biopsy would not have functioned.

LONG SEGMENT INVOLVEMENT

Female incidence is equal to that of males in the long segment type of aganglionosis.[1,16] Surprisingly, extent of disease correlates poorly with distress symptoms. Severe signs of obstruction have been frequent in low sigmoid levels, with milder signs in levels from the splenic or hepatic flexures or even the entire colon.

Total colonic and terminal ileal aganglionosis has been reported in detail previously.[1] Our last 3 patients were correctly diagnosed preoperatively on the basis of signs and symptoms of intermittent small bowel obstruction and roentgen studies showing either small bowel intussusception or a colon of normal caliber but shortened length[5] (Fig. 7, *A*, *B* and *C*). It is difficult to understand that patients can live weeks to months without colon ganglion cells,[5,8] presenting only with moderate postprandial emesis suggestive of pyloric stenosis or midgut rotation disorders to clinicians and surgens. If barium emena studies on such patients (commonly done to determine cecal position in possible malrotation cases) are performed for the purpose of excluding aganglionosis, the short length of the colon and the stasis seen on delayed roentgenograms may suggest the diagnosis if the examination is done at a time when obvious

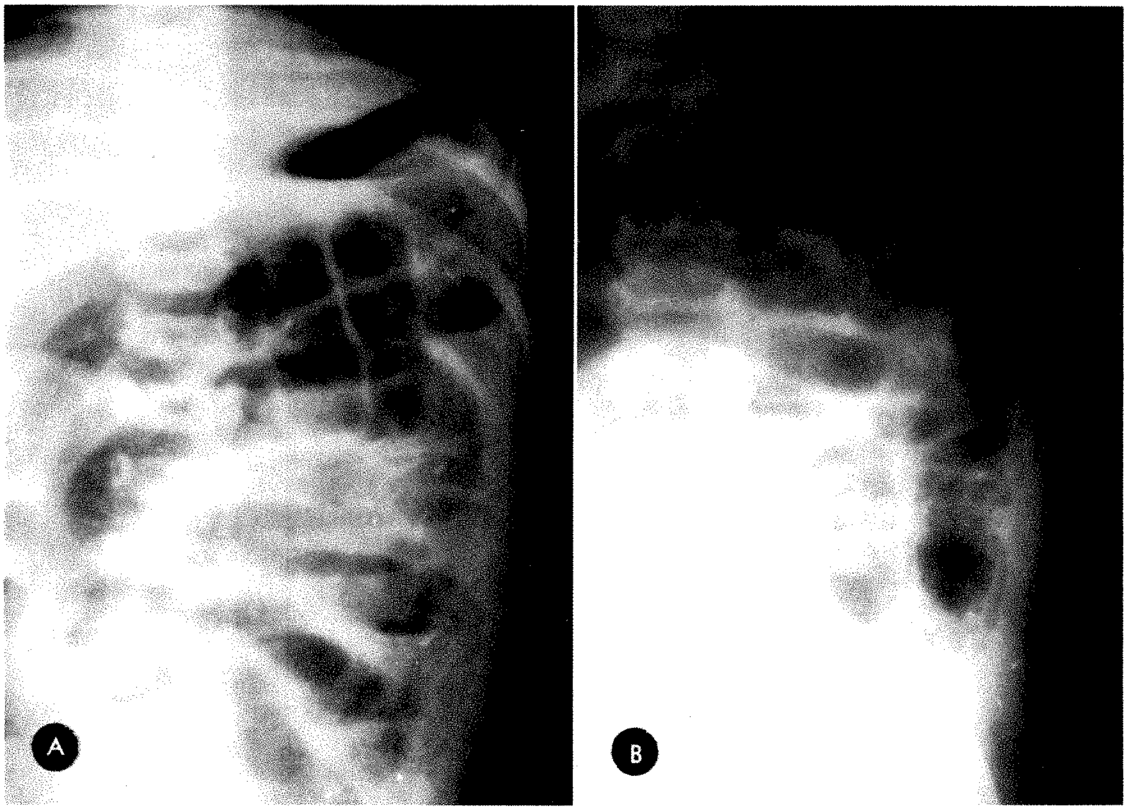

FIG. 6. Case 1. (*A*) Three day old girl with jaundice and bile emesis. Plain roentgenogram shows mild distention and extraluminal air paralleling the colon (pneumatosis intestinalis). (*B*) Close-up of descending colon shows lucent bubbles and strips outside the colonic lumen. Laparotomy was promptly undertaken in search of resectable gangrenous bowel. However, nothing abnormal was found and no biopsy was taken.

small bowel decompensation is absent. Massive distention of the small bowel usually constitutes operative indication; such distention, with a normal caliber colon, suggests aganglionosis.

THE NECROTIZING ENTEROCOLITIS OF HIRSCHSPRUNG'S DISEASE

The older infant or child with megacolon is the survivor of a disease that is fatal in up to 50 per cent of infants who develop enterocolitis.[3,6,8] The pattern of such colitis is fairly distinct. Marked distention (Fig. 8) develops despite the administration of enemas and suppositories. Constipation is replaced by foul diarrhea. High fever is present, although subnormal temperatures have also been reported. Enema tubes and intravenous fluids may aid the infant in recovering from the first attack, but subsequent attacks may prove fatal in days to even hours.

According to Bill and Chapman,[3] the process appears to be related to partial obstruction of the colon by the aganglionic segment. The colitis usually ends distally at the approximate "transition" segment. The involved bowel (the ganglionic bowel) is dilated, with denuded mucosa and pseudomembrane, and contains large amounts of electrolytes and fluid. Pathogenic bacteria have not been found, and the cause is not known. Many infants develop an attack following an apparently viral respiratory infection; however, viral studies have been negative.

No infant in the present series developed such colitis after diagnosis and prompt colostomy; *i.e.*, the disease can be avoided.[3,8] The performance of a colostomy

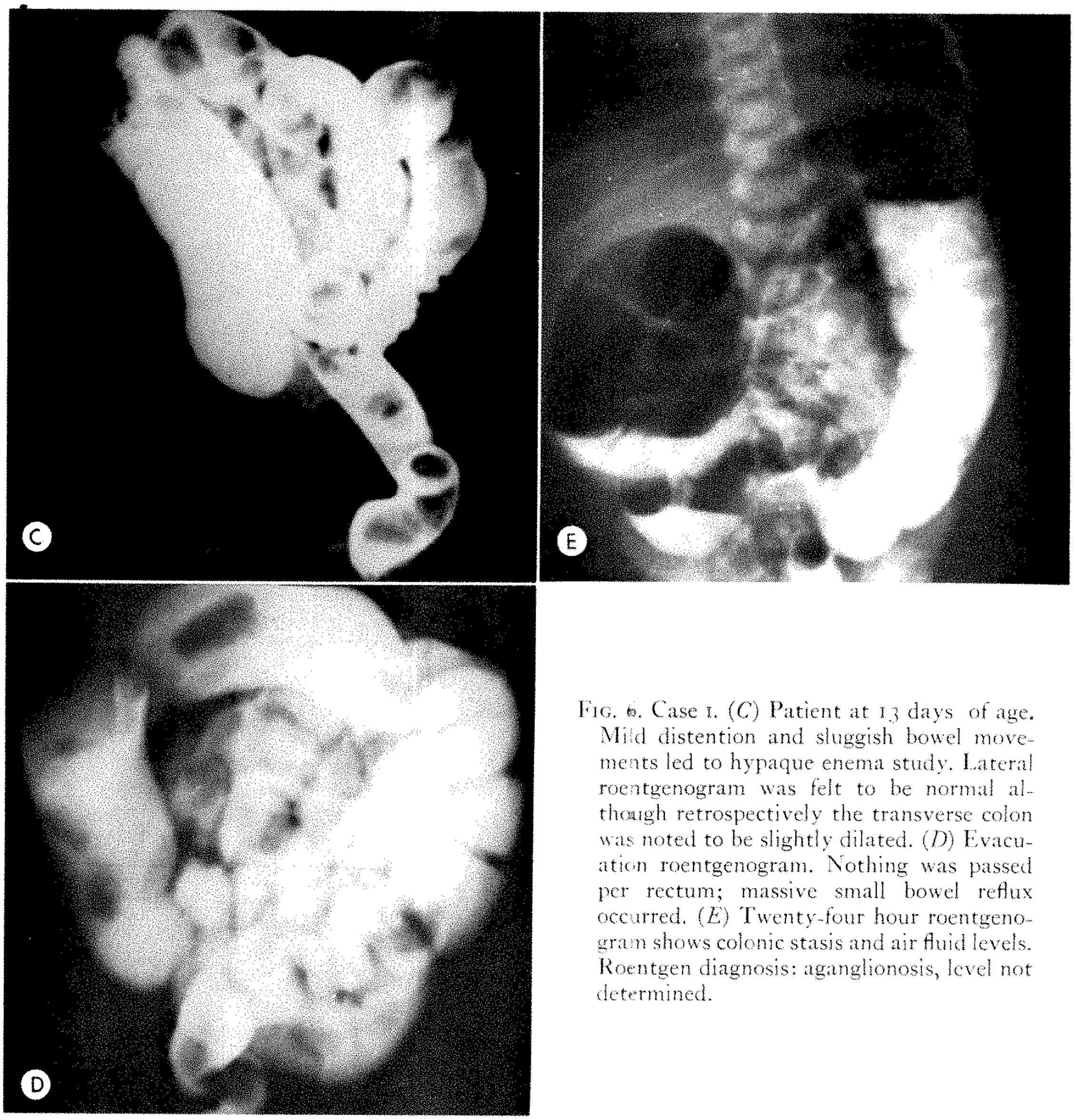

FIG. 6. Case I. (*C*) Patient at 13 days of age. Mild distention and sluggish bowel movements led to hypaque enema study. Lateral roentgenogram was felt to be normal although retrospectively the transverse colon was noted to be slightly dilated. (*D*) Evacuation roentgenogram. Nothing was passed per rectum; massive small bowel reflux occurred. (*E*) Twenty-four hour roentgenogram shows colonic stasis and air fluid levels. Roentgen diagnosis: aganglionosis, level not determined.

during an attack of colitis may lead to a high mortality rate.[3] Seven of our patients succumbed to colitis in the first weeks of life within hours of colostomy. A colostomy therefore should be performed, when aganglionosis is diagnosed by roentgen studies and frozen section biopsy at laparotomy, before colitis has developed.[3,6,8,16]

ILLUSTRATIVE CASE

CASE II. A male infant was distended and vomited bile in the first 48 hours of life. Digital rectal examination produced passage of meconium and relief of distention and the child was discharged from the nursery. At 6 days of age, distention recurred; at 8 days, bowel movements decreased; at 10 days diarrhea and fever were noted and lethargy increased until the 12th day when the child became moribund. At that time plain roentgenograms and barium enema studies (Fig. 9) showed an ulcerated dilated colon with a normal appearing rectosigmoid. Delayed roentgenograms were not available to evaluate stasis. At 14 days the infant was transferred to Babies Hospital but arrived in a terminal state with cyanosis and gasping. He died within several minutes of arrival. At post-

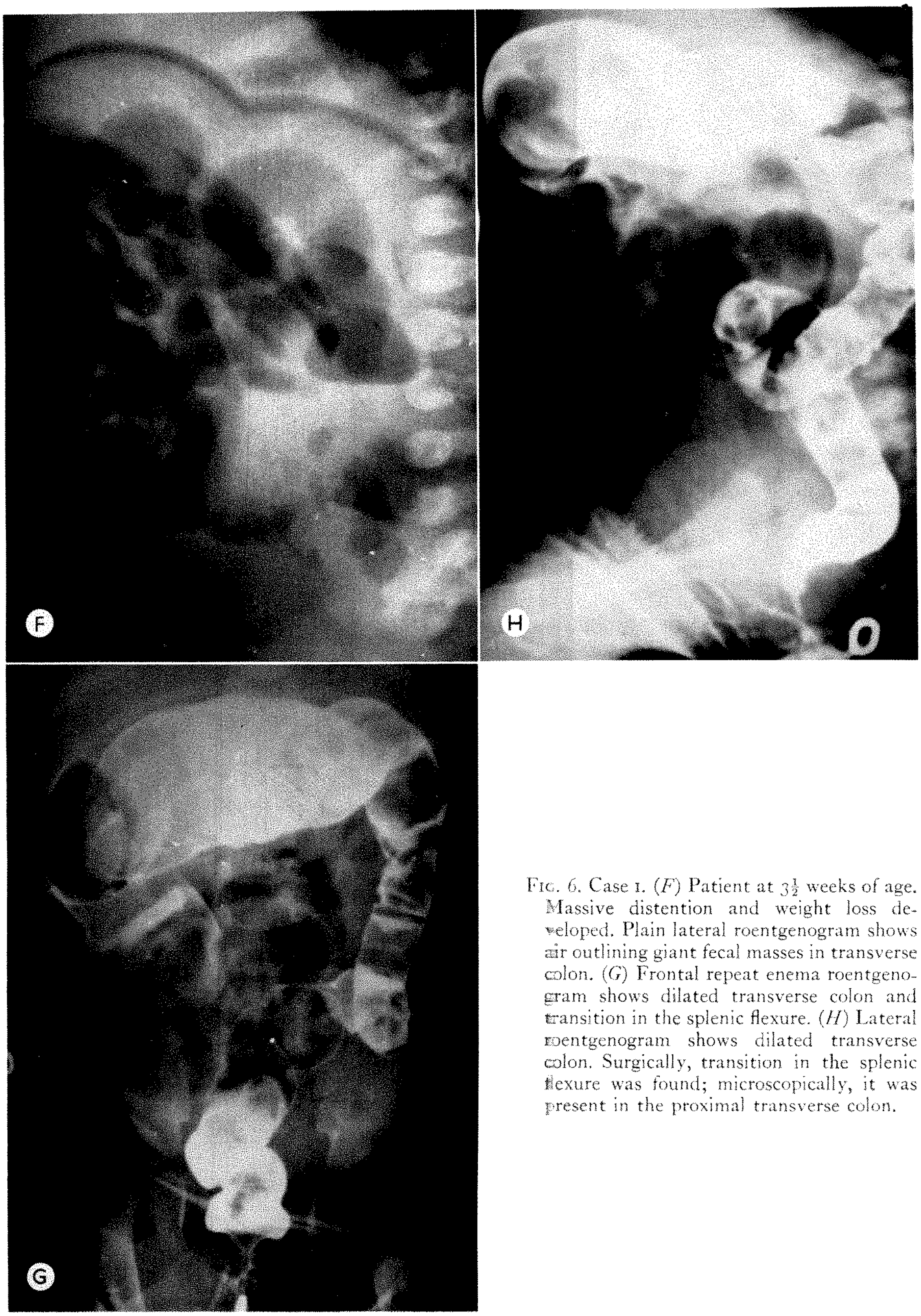

FIG. 6. Case 1. (*F*) Patient at $3\frac{1}{2}$ weeks of age. Massive distention and weight loss developed. Plain lateral roentgenogram shows air outlining giant fecal masses in transverse colon. (*G*) Frontal repeat enema roentgenogram shows dilated transverse colon and transition in the splenic flexure. (*H*) Lateral roentgenogram shows dilated transverse colon. Surgically, transition in the splenic flexure was found; microscopically, it was present in the proximal transverse colon.

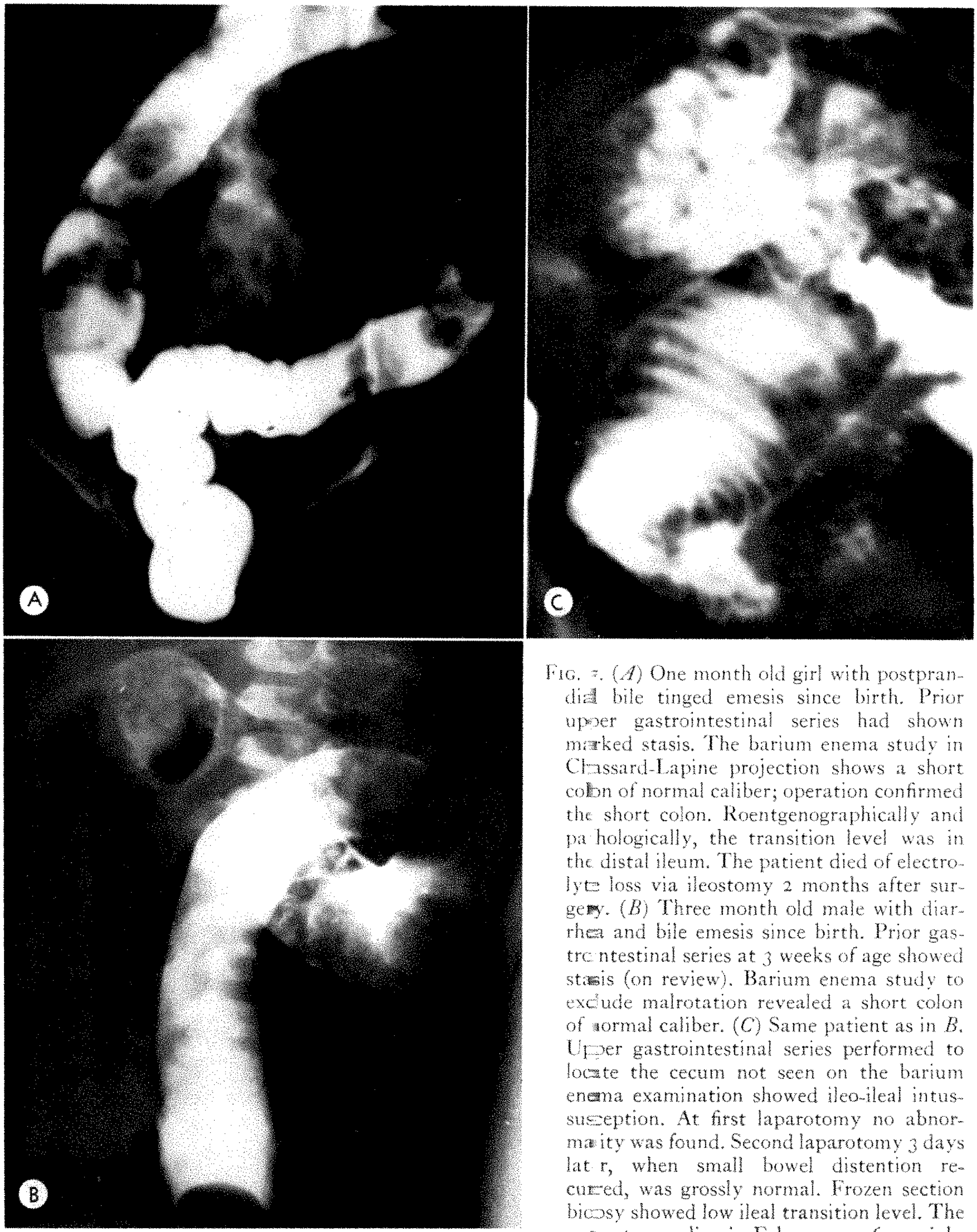

Fig. 7. (*A*) One month old girl with postprandial bile tinged emesis since birth. Prior upper gastrointestinal series had shown marked stasis. The barium enema study in Chassard-Lapine projection shows a short colon of normal caliber; operation confirmed the short colon. Roentgenographically and pathologically, the transition level was in the distal ileum. The patient died of electrolyte loss via ileostomy 2 months after surgery. (*B*) Three month old male with diarrhea and bile emesis since birth. Prior gastrointestinal series at 3 weeks of age showed stasis (on review). Barium enema study to exclude malrotation revealed a short colon of normal caliber. (*C*) Same patient as in *B*. Upper gastrointestinal series performed to locate the cecum not seen on the barium enema examination showed ileo-ileal intussusception. At first laparotomy no abnormality was found. Second laparotomy 3 days later, when small bowel distention recurred, was grossly normal. Frozen section biopsy showed low ileal transition level. The patient was alive in February, 1964, weighing 10 pounds at age of 17 months. Further surgery to aid absorption by a side-to-side anastomosis of the normal ileum to the aganglionic colon is contemplated.

mortem examination, the transition was found in the rectosigmoid both in terms of caliber of the colon and margin of cessation of the pseudomembranous enterocolitis. The ganglion cell transition was several centimeters proximal in the distally dilated sigmoid.

Comment. This case represents the infantile equivalent of the "toxic megacolon" of ulcerative colitis with a fatal outcome. Early diagnosis and a functioning colostomy alone would have prevented this.

DIFFERENTIAL DIAGNOSIS

Unlike the case of the older infant or child with aganglionosis, chronic constipation is not the main alternate diagnosis.

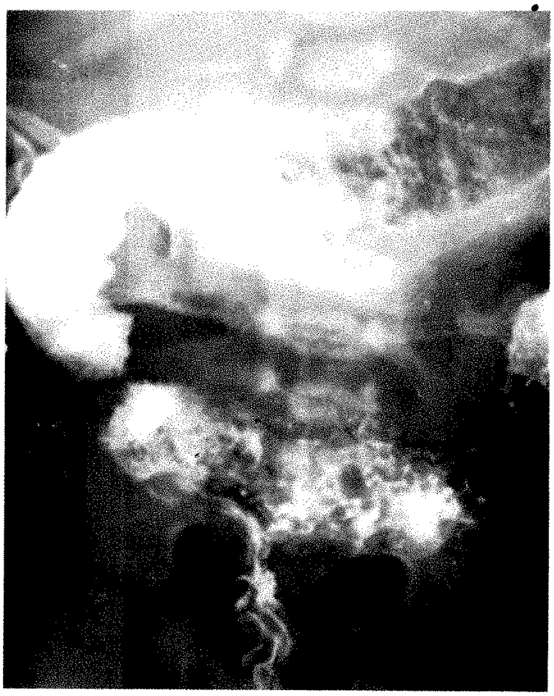

Fig. 9. Case II. Twelve day old male infant with early signs of constipation replaced by diarrhea, fever, and collapse between the 7th and 12th day of life. Barium enema roentgenogram on the 12th day of life shows the distended colon to the low sigmoid with spiculated irregular margins suggesting ulceration. The patient died on the 14th day of transfer to Babies Hospital. Microscopically and grossly, the transition differed by several centimeters, the gross level being more distal. Enterocolitis with necrosis extended from the cecum to the approximate level of the gross transition.

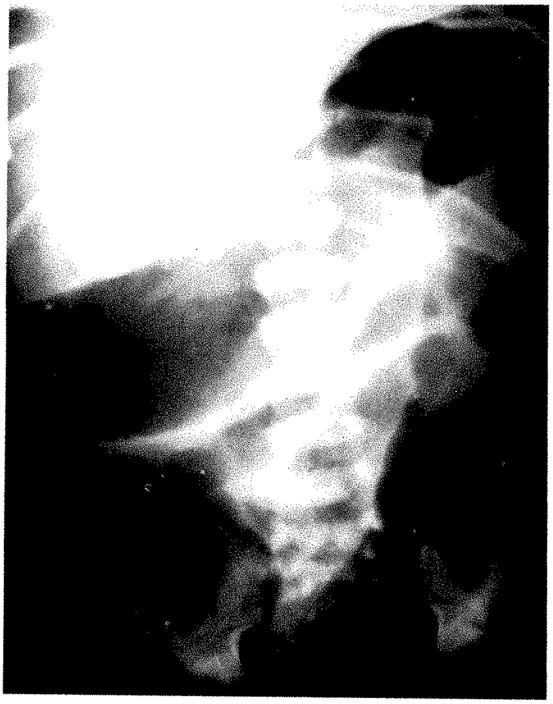

Fig. 8. Six day old male with constipation and distention on the first 4 days of life, followed by fever, diarrhea and prostration. Death occurred before colostomy could be done. The level of transition was in the sigmoid with necrotizing enterocolitis from the cecum to the low sigmoid. Plain roentgenogram shows giant colon loops with thick appearing walls.

The pattern of neonatal intestinal obstruction that is seen could be due to many organic causes, including small bowel atresia, malrotation with or without volvulus, and meconium ileus. Plain roentgenograms may clearly reveal the colonic distention and allow exclusion of these diagnoses. Barium enema study is of definitive value. The colon size is of differential diagnostic significance, since in Hirschsprung's disease the microcolon associated with small bowel atresia is absent.[1] In malrotation there is a normal evacuation pattern and cecal displacement is seen. Total colonic aganglionosis has been found to present a colon of normal caliber rather than the microcolon seen in small bowel distention.[1]

The meconium plug[7,24] syndrome should

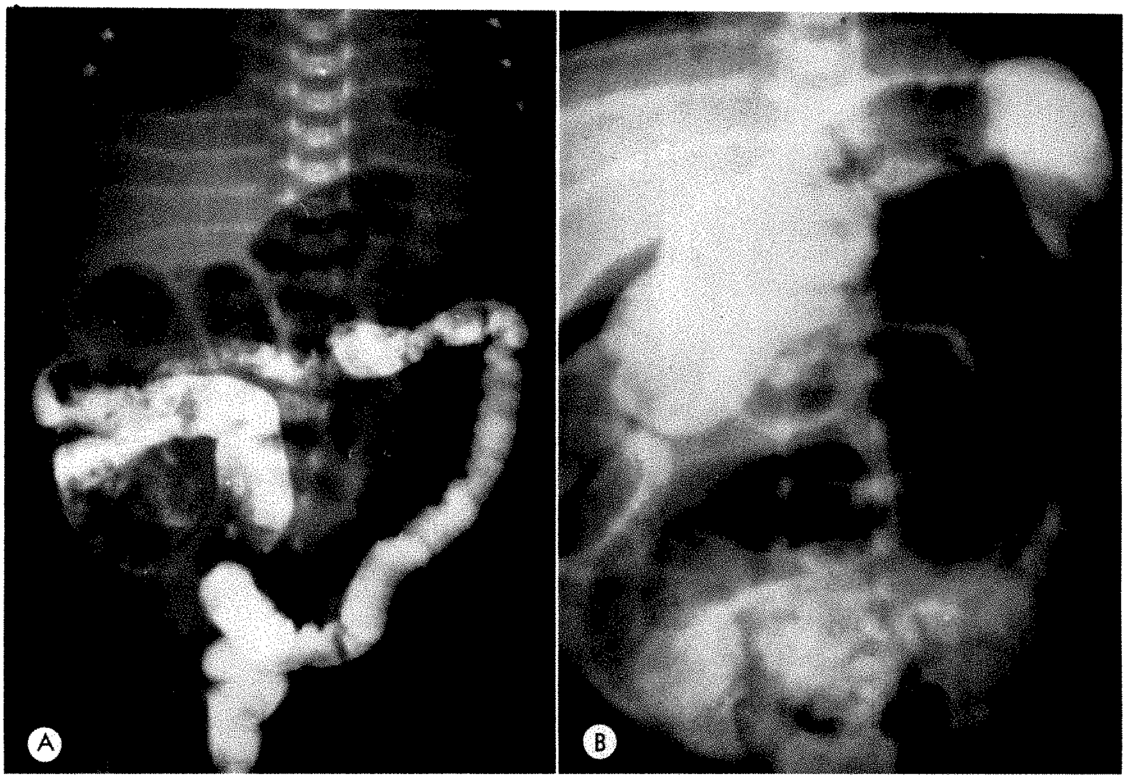

Fig. 10. (*A*) Thirty day old premature infant with alternating diarrhea and constipation from the first day of life until death which occurred the day of the barium enema examination. Enema study shows a dilated small bowel and a slightly short colon of normal caliber. A diagnosis of possible total aganglionosis was made. Cecal defect suggested possible ileocolic intussusception. Postmortem examination revealed a gangrenous cecum and ileum with abscess in the right lower quadrant and normal ganglion cells. (*B*) Ten day old premature infant with distention and bile emesis. The patient had stooled normally in the first days of life. Plain roentgenograms and barium enema study showed a caliber change in the proximal left colon and a dilated small bowel. A diagnosis of aganglionosis was made. At laparotomy, a perforated midtransverse colon and ileum, sepsis, and normal ganglion cells were found. The "pseudotransition" was seen at operation, but at necropsy the left colon was normal.

be considered in the differential diagnosis when signs of obstruction appear in the newborn period. With relief by digital examination or cleansing enema, a barium enema study will disclose a large plug of obstructing meconium usually high in the colon and a collapsed ribbon-like left colon. Characteristically, repeat enema studies show return of the left colon diameter to normal and no evidence of stasis on the late roentgenograms. Two of 9 patients so diagnosed in previous years at Babies Hospital returned in months with obvious aganglionic megacolon. The diagnosis of meconium plug syndrome should be made only after aganglionosis has been excluded.

The most confusing cases in the differential diagnosis are the patients with "sepsis,"[18,23] a category that includes necrotizing enterocolitis, alone or with obvious pulmonary and central nervous system infection, with a high incidence of premortem and even higher postmortem positive blood cultures. The patients are distended and vomit bile. The distention is visualized on plain roentgenograms, while a barium enema study may show a colon of normal caliber (Fig. 10*A*), raising the question of total aganglionosis of the colon or a pseudotransition (Fig. 10*B*). The surgical findings have ranged from distention to peritonitis, enterocolitis, bowel perforation and portal vein gas. The ganglion cell supply is normal.

Helpful differential points are:

A. *Age.* The vast majority of patients with sepsis and abdominal signs of obstruction are premature infants; aganglionosis is almost exclusively a disease seen in full term infants.

B. *Onset of Signs and Symptoms.* Patients with aganglionosis appear distended at 48 to 72 hours after birth though they are not especially ill in appearance. Patients with sepsis generally have a 3 to 5 day period of doing well, then apneic episodes develop. In many, blood is passed per rectum and there is onset of distention. Of all patients with neonatal distention, this group is the most difficult to differentiate from aganglionosis.

SUMMARY

Aganglionosis, or Hirschsprung's disease, has its onset in the newborn period. The resemblance of its clinical and roentgenographic features to obstructive signs and evidence of colonic distention and stasis reflect the abnormal physiologic nature of the aganglionic bowel.

Definitive diagnosis is possible in the vast majority of cases at this time. With prompt detection and relief of obstruction by adequate colostomy, the extremely grave and often lethal complication of enterocolitis can be avoided.

Emphasis is placed on the physiologic observations of the altered colon rather than on the morphologic studies of the transition from normal to aganglionic bowel.

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THE ROENTGENOLOGY OF NEONATAL ABDOMINAL MASSES*

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THE discovery of an abdominal mass in a newly born infant is an uncommon and somewhat alarming event. Nevertheless, a review of 117 such cases shows that most of these babies, who present a challenging differential diagnosis, do well. Although a surprising number of conditions can cause abdominal masses in the newborn period, this series suggests several generalizations:

(1) More than half of the masses are of renal origin. Multicystic kidney disease (the most common diagnosis) and hydronephrosis together account for almost 40 per cent of the cases.

(2) Few of these masses are malignant. Neuroblastoma and Wilms' tumor, the usual abdominal neoplasms of childhood, are uncommon in the newborn period and, when found, respond more satisfactorily to treatment than in older children.

(3) Significant congenital disease elsewhere is quite likely in a case of hydrocolpos or hydrometra, is fairly likely in a case of polycystic kidney disease, is less common with hydronephrosis and multicystic kidney, and is unlikely in a newborn with an ovarian cyst, a hepatobiliary mass, a duplication, a Wilms' tumor, or a neuroblastoma.

(4) A mobile anterior midline mass is apt to be a duplication or an ovarian cyst. A midline mass arising from, and fixed to, the pelvis is generally a hydrometra, a hydrocolpos, or an enlarged bladder.

(5) If intestinal obstruction is present, the mass is likely to be of gastrointestinal origin, unless it is a hydrocolpos or hydrometra and the obstruction is due to an associated imperforate anus. Other extra-alimentary masses, no matter how large, seldom obstruct.

(6) Most cases of multicystic kidney are found during the first 2 days of life. Hydrometra, hydrocolpos, and infantile ovarian cysts also are usually discovered in the first 48 hours, whereas abscesses are unlikely to present as abdominal masses before the age of 1 week.

(7) The outlook for a newborn with an abdominal mass is fairly good. With intravenous urography playing a key role, an astute roentgenologic approach to the problem will often lead to the correct diagnosis. Laparotomy will generally be indicated. About 60 per cent of these patients can be surgically cured, one fifth can be helped by surgery or appropriate medical management, and the remainder will die in early life from their disease, its complications, or associated conditions. An aggressive approach to these problems must be followed. Waiting for the newborn to grow, for the mass to disappear, or for the child to die cannot be defended.

DIAGNOSTIC METHODS

After careful abdominal palpation,[22] inspection of the perineum, and urinalysis, the preoperative differential diagnosis will rest on the roentgenologic examination. Plain roentgenograms of the abdomen are always warranted. A lateral view of the abdomen sometimes reveals a mass that is invisible in the anteroposterior projection. Intravenous urography should almost always be performed, generally with oblique and lateral projections. If the plain roentgenograms and clinical data suggest malignancy, injection via a leg vein will allow visualization of the inferior vena cava, for evaluation of venous displacement, invasion, or obstruction by tumor (Fig. 14). Occasionally, the situation will call for cystography, retrograde pyelography, a barium enema study, an upper gastrointestinal series, or vaginography. A preoperative survey of the long bones for metastases is usually not indicated.

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The total body opacification principle[18] is often helpful in the performance and interpretation of intravenous urography in these cases. Intravenously injected contrast material mixes with the plasma and rapidly distributes itself throughout the arteries, capillaries and veins. The entire body, therefore, becomes slightly opaque, and the added radiodensity of an organ will be proportional to the volume of blood it contains. Normal kidneys, which receive about 20 per cent of the cardiac output, would be expected to be selectively opacified even without concentration of contrast material in the urine being formed. Fat, scantily supplied with blood, will receive relatively little added radiodensity and should contrast more clearly with nearby water-density tissue; this latter effect has been repeatedly observed in practice. Only slowly, if at all, will contrast material enter avascular structures, such as cysts, hematomas, infarcted organs, abscess cavities, areas of necrosis, the ventricles of the brain, fluid-filled serosal cavities, or the lumina of hollow viscera, always excepting urinary opacification. An early roentgenogram will then show these avascular structures as less dense areas surrounded by opacified tissue.

Since the appreciation of the principle of total body opacification,[18] the effect—with the avascular lesion appearing as a negative shadow—has been recognized, in retrospect or in the diagnosis of current cases, in urograms of patients with various cystic tumors and masses (Fig. 1, *A* and *B*), in hepatic and adrenal hemorrhages, in necrotic tumors, in hepatic abscesses, in massive hydronephrosis, in renal vein thrombosis with infarction, in ascites, and in midgut volvulus with infarction. The phenomenon is more useful in infants and young children than in adults, because scatter from large volumes of tissue will often obliterate the relatively slight differences in opacity, be-

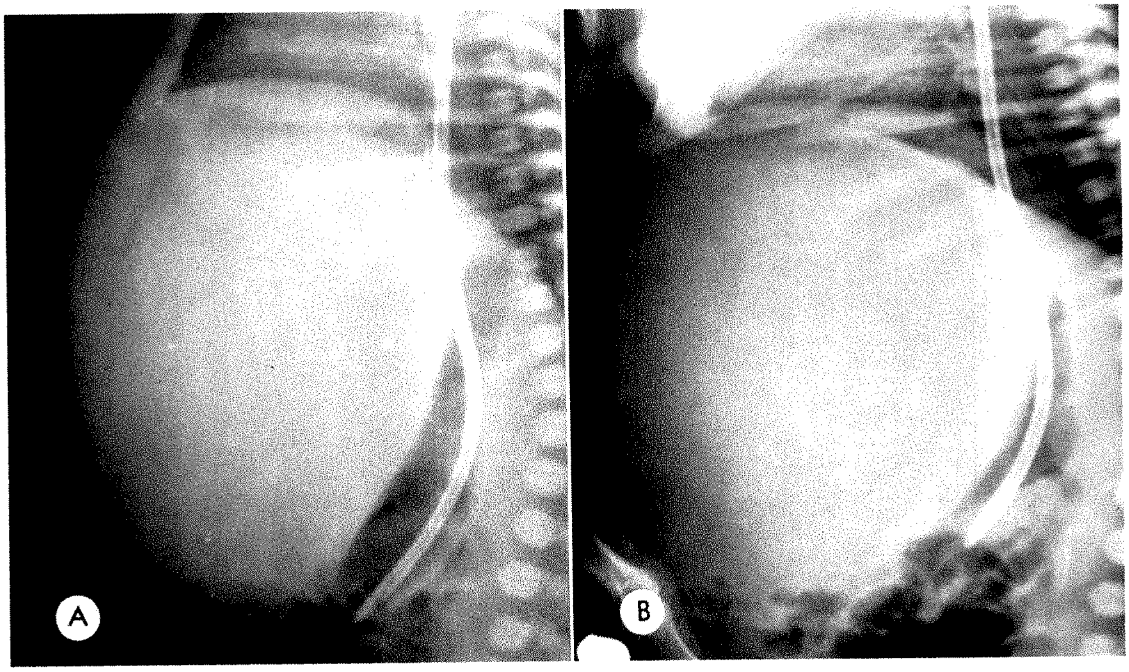

Fig. 1. (*A*) Nonopacification of an avascular mass, shown 10 minutes after injection for urography, and especially evident by comparison with (*B*) the preliminary lateral view of the abdomen. The margin between the nonopacified lesion and the normally opacified liver tissue can be seen 1–2 cm. in front of the nasogastric tube. This was a 12 cm. solitary cyst of the anterior portion of the liver; the child was 1 day old.

cause children's lesions are often relatively larger, and because relatively large volumes of contrast material can be used routinely. At the Children's Hospital Medical Center, the current practice is to use 10 cc. of renografin 60 for a full-term newborn's intravenous urography, the early films of which are then scanned for the total body opacification effect. In order to allow careful point-to-point comparison of densities, factors of technique must not vary during the examination. Occasionally, a lesion will not be seen on the preliminary roentgenogram, will appear as a negative shadow a few minutes after injection, and then will slowly disappear as the kidneys extract the contrast material from the blood.

Since more than three-quarters of neonatal abdominal masses are cystic or otherwise avascular, total body opacification is widely useful in their differential diagnosis. The effect can be perceived in most avascular masses greater than 5 cm. in diameter. In the present series of neonatal masses, the effect was commonly seen in multicystic kidneys and ovarian cysts. Some severely hydronephrotic kidneys showed the effect transiently. The cases of mesenteric cyst, hepatic cyst, and choledochal cyst all revealed their avascular nature by means of this phenomenon. The effect was also seen in two cases of polycystic disease and in single cases of Wilms' tumor with necrosis and cyst formation, intestinal duplication, cystic intestinal dilatation proximal to ileal atresia, and midgut volvulus with infarction.

CASE MATERIAL

One hundred and seventeen cases of abdominal masses discovered in the newborn period—the first 28 days[10] or first month[17] of life—were found in the Children's Hospital Medical Center files of the last 20 years. A review of these records and their roentgenograms (available in 103 cases, reports available in all) is the basis of the present report. The abdominal mass was the chief manifestation in most cases, and in many cases it was the only historical point and only physical finding. This review includes most of the cases reported several years ago from the surgical point of view by Longino and Martin.[11] With the exception of the ectopic kidneys and several of the polycystic kidneys, all the cases have been proven at surgery or autopsy.

The following groups were excluded:

(1) Newborns presenting with enlarged bladders, due to lower urinary obstruction, but without palpably enlarged kidneys. The nature of such masses is readily shown by their collapse upon catheterization.

(2) Newborns with absent abdominal wall musculature with hydronephrosis,[16] the diagnosis in this distinctive group being evident on inspection.

(3) Newborns with abdominal masses but in whom no roentgenograms were taken. This group includes newborns with severe polycystic kidney disease, dying too soon for study; cases of hydrocolpos with imperforate hymens bulging sufficiently to make the diagnosis obvious; and several cases of intestinal duplication.

(4) Newborns with hepatosplenomegaly, as in erythroblastosis or congestive heart failure, without suspicion of intrahepatic or other abdominal masses.

(5) Hypertrophic pyloric stenosis tumors.

(6) Pelvic tumors palpable only by rectum, not abdominally; these were mostly teratomas.

(7) Cases of intestinal obstruction in which palpable bowel loops had some of the physical characteristics of a mass but in which the diagnosis of obstruction without true mass was clear nevertheless.

The incidence of the various neonatal masses is given in Table I. The figures will convey some idea of the spectrum seen in an active newborn service and will afford physicians faced only occasionally with this problem an impression of the diagnostic probabilities. A contrasting breakdown of the types of abdominal masses found throughout all of childhood by a pediatric urology service has recently been presented.[15] No example of adrenal hemorrhage[2]

TABLE I

NEONATAL ABDOMINAL MASSES

	Found in First 2 Days of Life	Found in Rest of First 4 Weeks	Total
Renal Masses			
Multicystic dysplastic kidney	20	5	25
Hydronephrosis	10	10	20
Polycystic kidney	3	4	7
Wilms' tumor	4	1	5
Renal ectopia	1	3	4
Renal vein thrombosis	1	0	1
Benign cystic hamartoma	0	1	1
Total	39	24	63
Gastrointestinal Masses			
Intestinal duplication	3	8	11
Malrotation, volvulus	1	1	2
Meconium ileus with peritonitis or volvulus	2	0	2
Omental cyst, mesenteric cyst	2	0	2
Colonic leiomyosarcoma	0	1	1
Cystic ileal dilatation proximal to atresia	1	0	1
Total	9	10	19
Genital Masses			
Hydrocolpos, hydrometra	9	0	9
Ovarian cyst	6	0	6
Total	15	0	15
Hepatobiliary Masses			
Solitary liver cyst	2	0	2
Choledochal cyst	0	1	1
Cholecystitis and hydrops	0	1	1
Hepatoma	1	0	1
Total	3	2	5
Nonrenal Retroperitoneal and Extraperitoneal Masses			
Neuroblastoma	5	4	9
Abscess	0	4	4
Teratoma	2	0	2
Total	7	8	15
Grand Total	73	44	117

presenting as a neonatal mass could be found in the hospital files, and none of the following additional conditions was discovered as an abdominal mass in the newborn: solitary renal cyst, urachal cyst, sarcoma botryoides, neurenteric cyst, anterior meningocele, chordoma, lymphoma, leukemia, and lipoma.

FINDINGS ON PLAIN ROENTGENOGRAMS

The great majority of these masses was evident, by virtue of displacement of gas-containing bowel or stomach, on plain roentgenograms of the abdomen. All of the large masses were readily seen. Sometimes a smaller mass, especially a posterior mass, could be seen in the lateral view but not in the anteroposterior projection. Occasionally, a small mass was represented merely by a slight local paucity of intestinal gas. Large masses sometimes bulged the flanks, raised one or both diaphragmatic leaves, or produced obvious ventral protuberance in the lateral view. Calcium could be seen in the case of infarcted intrauterine volvulus, in the hepatoma, in the 2 cases of intrauterine meconium peritonitis, in 3 of the 9 neuroblastomas (Fig. 13), and the teratomas contained bones (Fig. 15 and 16); otherwise these masses were of uniform water density on the plain roentgenograms. No mass produced erosion or indentation of nearby bones. No pulmonary or bony metastases were found.

The renal masses, except for the cases of renal ectopy, were often large enough to protrude far forward toward the anterior abdominal wall. They displaced the stomach upward and medially and the intestines anteromedially. The presence of a flank mass on each side limited the differential diagnosis to polycystic kidneys (7 cases) and bilateral hydronephrosis (10 cases).

The ovarian cysts generally rose far out of the pelvis, and their pelvic origin was sometimes unclear. They lay on the side of the parent ovary or in the midline and were often fairly far anterior. The hydrocolpos and hydrometra generally were fixed in the midline. The hepatic and biliary masses were all in the right upper quadrant and appeared to be contiguous with the liver. The signs of obstruction often dominated the plain roentgenograms of infants with gastrointestinal masses.

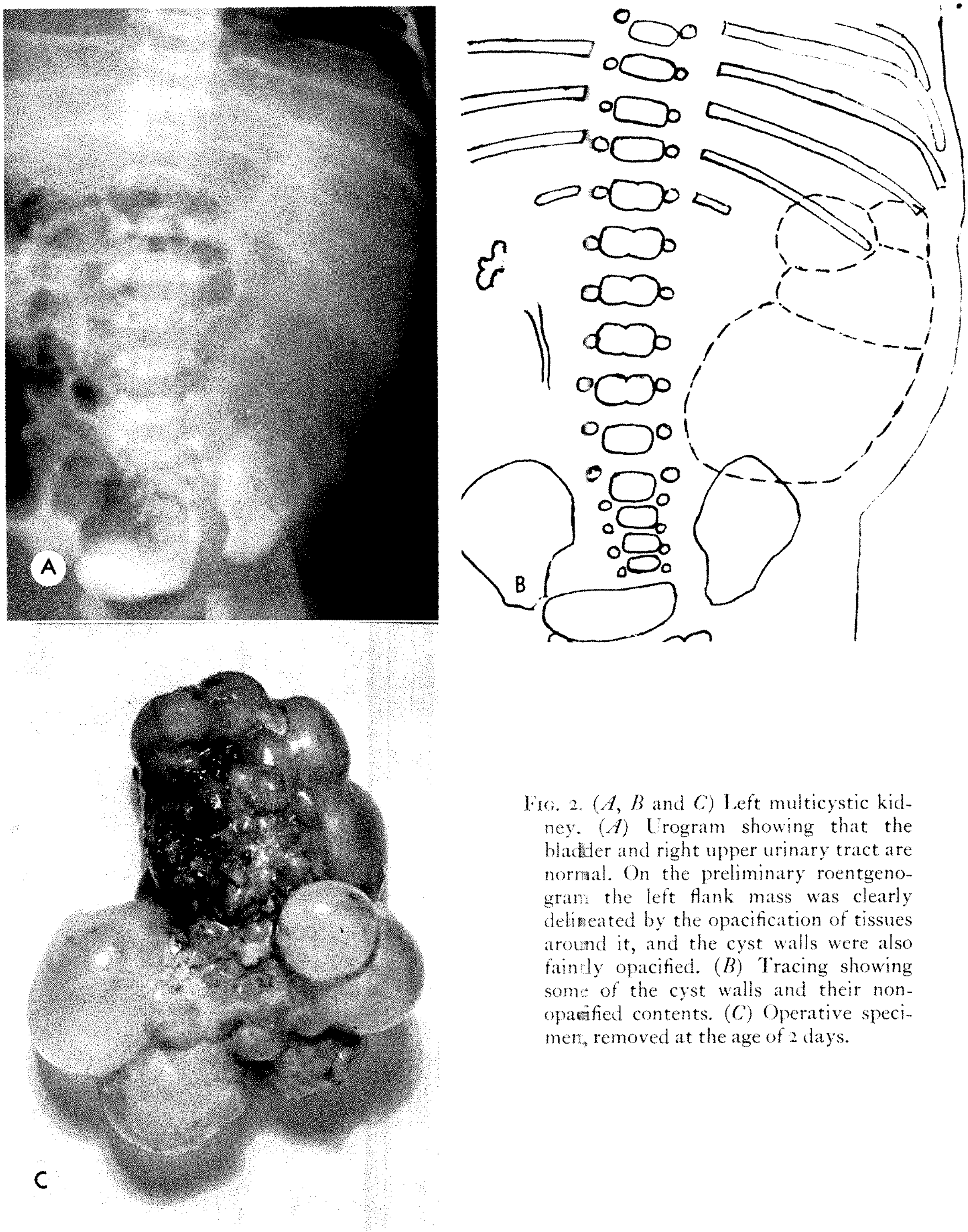

Fig. 2. (*A*, *B* and *C*) Left multicystic kidney. (*A*) Urogram showing that the bladder and right upper urinary tract are normal. On the preliminary roentgenogram the left flank mass was clearly delineated by the opacification of tissues around it, and the cyst walls were also faintly opacified. (*B*) Tracing showing some of the cyst walls and their nonopacified contents. (*C*) Operative specimen, removed at the age of 2 days.

The largest mass, a duplication, was 23 cm. long when removed, which is almost half of the total length of an average newborn child. Several masses had diameters of 12 cm. or more.

MULTICYSTIC DYSPLASTIC KIDNEY

Multicystic kidneys,[1,20] the most common lesions (Fig. 2 to 4, inclusive), are comprised almost entirely of large cysts, up to 6 cm. in diameter, with only a little solid

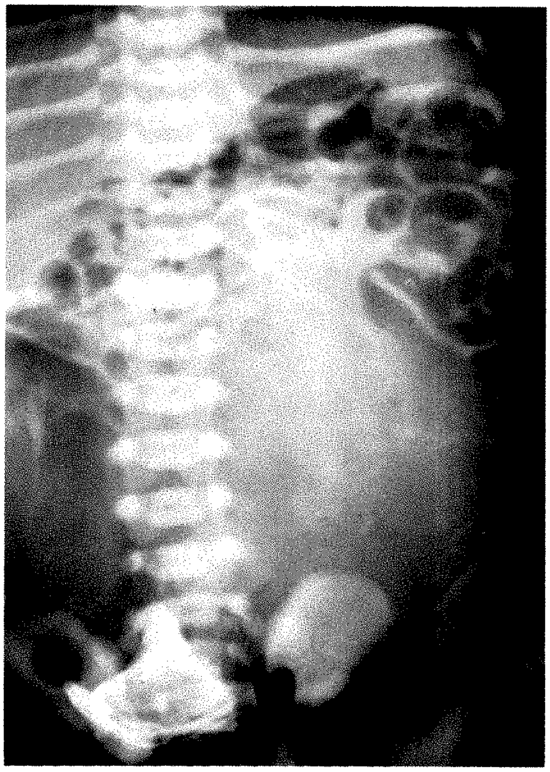

Fig. 3. Left multicystic kidney. The walls of the individual cysts are vascularized and have, therefore, become slightly opaque on this urogram. The cyst contents are nonopacified. Septate nonopacification in a flank mass at this age (the child was 1 day old) is diagnostic of multicystic dysplastic kidney.

tissue. In the gross, they are barely identifiable as kidneys. The ureters are often atretic and the pelvis may be poorly formed or unidentifiable. The fragments of solid tissue contain glomeruli in various stages of development and degeneration and also often contain cartilage. This kdney lesion is unilateral and is almost always found very early in life. No other organ is cystic, and the condition is not inherited. These findings contrast with polycystic kidney disease, which is bilateral, in which (in the newborn period at least) the cysts are generally less than 5 mm. in diameter, in which several organ systems are often affected, and in which there is a definite hereditary tendency.

Eighty per cent of the cases of multicystic kidney were found during the first 2 days of life. Multicystic disease occurred twice as often as hydronephrosis during that period; thereafter, hydronephrosis was more common. Seldom symptomatic and then only by reason of bulk, the multicystic kidney masses often felt lobular and sometimes transilluminated. They sometimes filled all of one side of the abdomen, from the ribs to the pelvis. They were sometimes soft and palpably cystic. They often produced considerable abdominal distention and prominence of the veins of the abdominal wall. The urinalysis was generally negative. Other congenital disease was not too frequent; among these 25 cases, tetralogy of Fallot, cystic hygroma of the neck, sagittal craniosynostosis, and cleft palate each occurred once. In 1 case there was involvement of half of a horseshoe kidney.

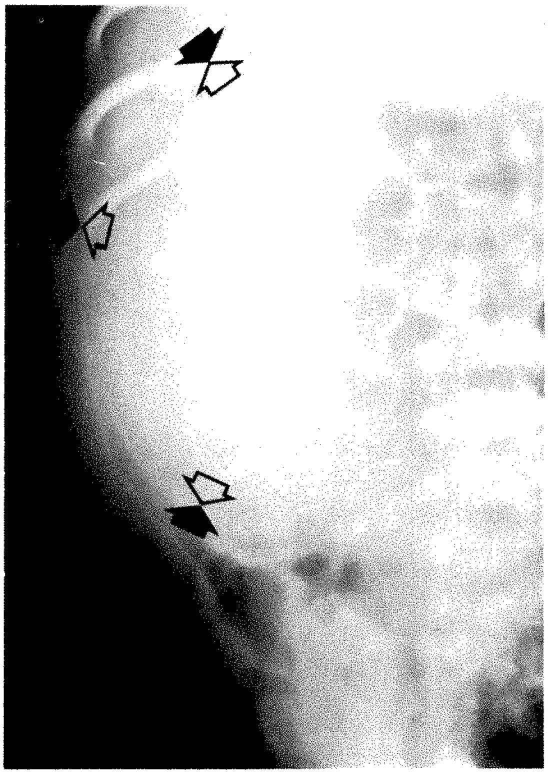

Fig. 4. Right multicystic kidney. This 30 minute urogram shows a large rounded nonopacifying mass abutting the liver. Removed at the age of 3 days, the kidney was composed of one large and several small cysts.

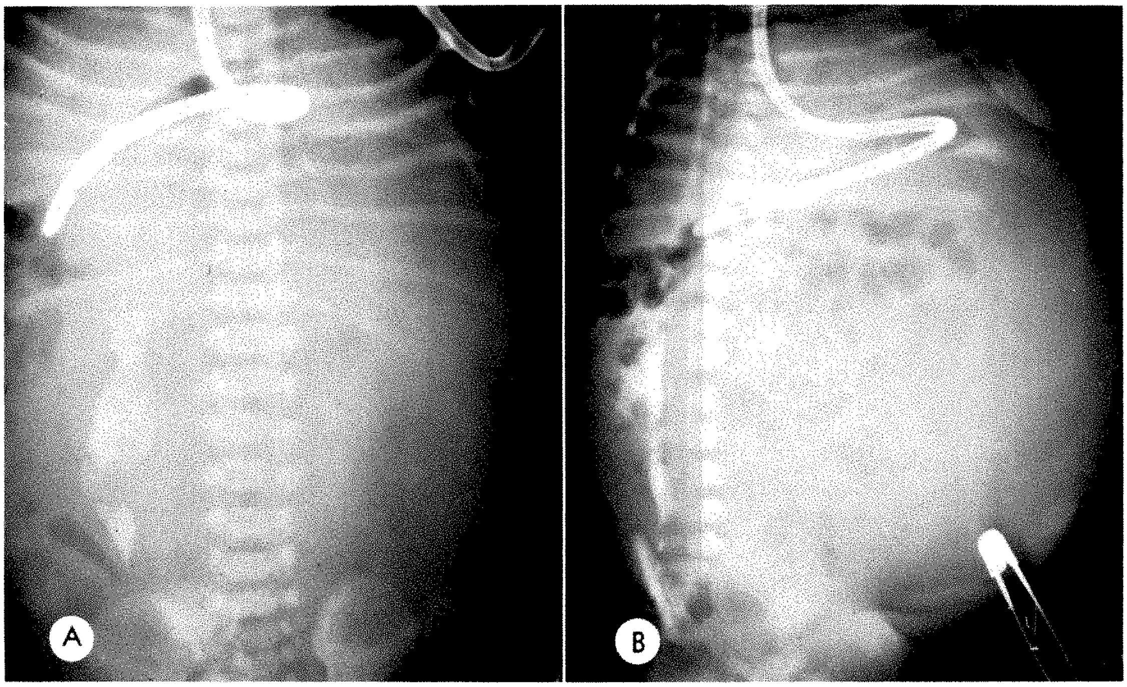

FIG. 5. (*A* and *B*) Left ureterovesical obstruction with hydronephrosis. The urine within the grossly dilated left upper tract remains lucent on these anteroposterior and oblique pyelograms, whereas the remainder of the body and especially the remaining rim of kidney tissue have become relatively opaque. The lower pole of the mass appears to have caused partial contralateral low ureteral obstruction. The mass was found at 1 hour of age and was removed 2 days later.

Intravenous urography revealed total failure of excretory function of the involved kidney. Many of these masses showed the total body opacification effect; that is, they remained relatively lucent on the early urograms, while the remainder of the body became more dense. Often the individual cysts were faintly seen as round lucent areas separated from each other by slightly opacified septa (Fig. 2*A*; and 3); this appearance in a flank mass is diagnostic of the condition. The opposite kidneys and ureters were normal, except for questionable partial contralateral low ureteral obstruction by the mass in one case. The bladder was often indented from above by the mass.

The treatment of choice is nephrectomy. Except for one boy who developed an apparently unrelated nephrotic syndrome at the age of 2, none of these cases, followed for various periods postoperatively, has had any further urinary problem.

HYDRONEPHROSIS

Hydronephrosis was the second most common lesion. Among the 20 cases were 6 newborns with ureteropelvic obstruction (bilateral at birth in 1 case, becoming evident on the other side at the age of 7 months in another), 1 patient with ureterovesical obstruction (Fig. 5, *A* and *B*), 7 with obstructing ureteroceles (Fig. 6, *A* and *B*), 3 sets of posterior urethral valves (Fig. 7), and 3 cases of bilateral hydronephrosis of uncertain cause. Five of the 6 cases of ureteropelvic obstruction were found before the infant was 24 hours old.

Half of the cases of hydronephrosis were found during the first 2 days of life, before infection had developed; at this stage there were generally no symptoms except those secondary to a bulky mass. In the cases found later in the neonatal period, infection had often caused fever, listlessness, anorexia, failure to thrive, or vomiting, and the urine generally contained erythrocytes, leukocytes, albumen or bacteria. The hydronephrotic kidneys generally felt smooth and varied from the boggy to the hard and tense. When there was urethral obstruction, a poor urinary stream or infrequent voiding was noted. An enlarged bladder was sometimes palpable in cases of lower tract obstruction. Once an obstructing ureterocele was visible at the vaginal introitus. Four of these 20 cases had several severe congenital defects.

The roentgenographic findings varied with the cause and severity of the hydronephrosis. In cases of severe hydronephrosis with negligible urine formation, the thinned and dilated kidney, in effect a urine-filled cyst, showed as a nonopacifying, globular, noncompartmented mass on the early urograms. With slightly less severe hydronephrosis, contrast material within the tubules of the remaining renal parenchyma could be seen outlining the hydronephrotic sac[4,13] (Fig. 5, *A* and *B*). The remainder of the hydronephrotic kidneys showed the more usual signs of hydronephrosis, with delayed appearance of contrast material, dilatation of the pelvis and calyces, and thinning of the renal parenchyma. When an ectopic ureterocele caused the obstruction, a selectively dilated upper pole sometimes gave the signs of an intrarenal mass. Ureteroceles were often visible as filling defects within the bladder on intravenous urograms (Fig. 6, *A* and *B*). Cystography showed ureteroceles, ureteral reflux, bladder neck obstruction, and posterior urethral valves (Fig. 7) when such were present.

Therapy has been much less successful in this group of cases. Two-thirds of the patients with bilateral hydronephrosis died in infancy. Of those with unilateral disease, about half now appear to be well, with the remainder either dead or bearing evidence of residual renal disease.

POLYCYSTIC KIDNEY DISEASE

Seven cases of the several varieties of

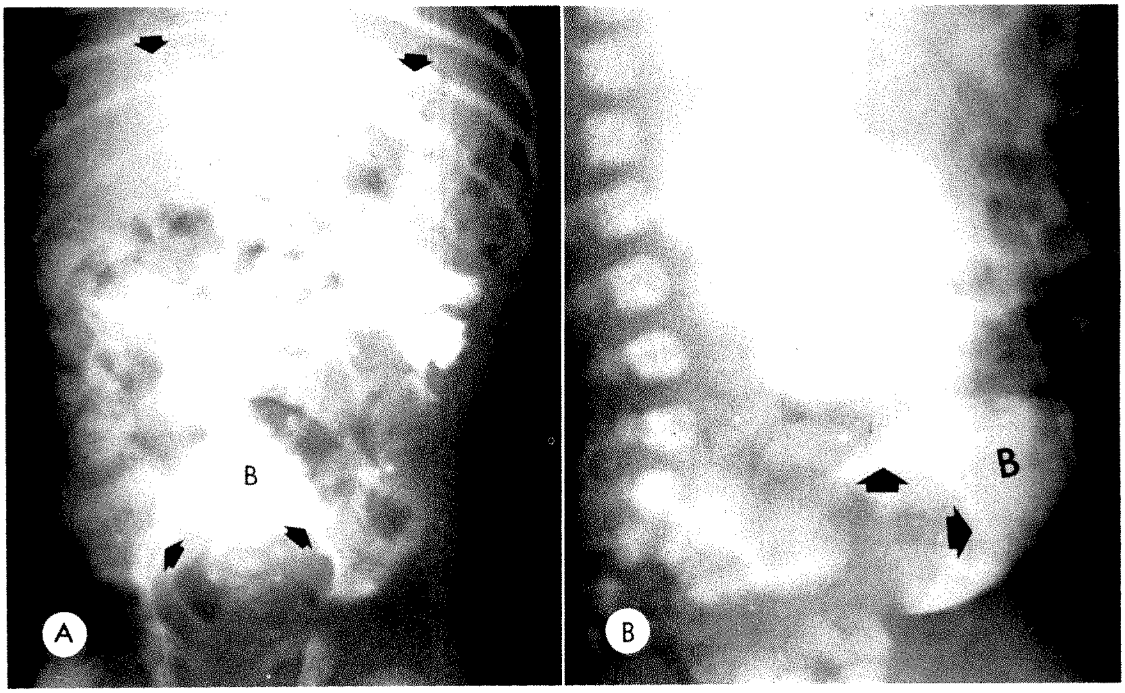

Fig. 6. (*A* and *B*) Bilateral hydronephrosis with bilateral double collecting systems and ureteroceles. These anteroposterior and lateral urograms show the ureteroceles as filling defects within the bladder (B). The upper sets of arrows on *A* outline the severely hydronephrotic upper poles, which on the preliminary roentgenograms could be seen as nonopacified masses. The masses were found at the age of 11 days.

polycystic renal disease[1] were found. Several of these newborns were investigated primarily because of failure to thrive. One infant's sibling had died of polycystic disease. Renal enlargement varied from moderate to extreme. Three of these cases had known congenital disease in other organs.

Pyelographic function varied from the poor to the almost normal. Cystic filling defects pressing upon the calyces and pelvis were suggested in only 1 case, although several cases showed less specific collecting system distortion. In 2 cases, which apparently represented the renal tubular ectasia category of cystic disease,[21] radially arranged nonopacifying shadows were seen in the early roentgenograms,[9] and dilated distorted tubules were seen in the later phases or on retrograde study (Fig. 8). Caliectasis, pyelectasis, and ureterectasis were not found. Renal enlargement was always bilateral.

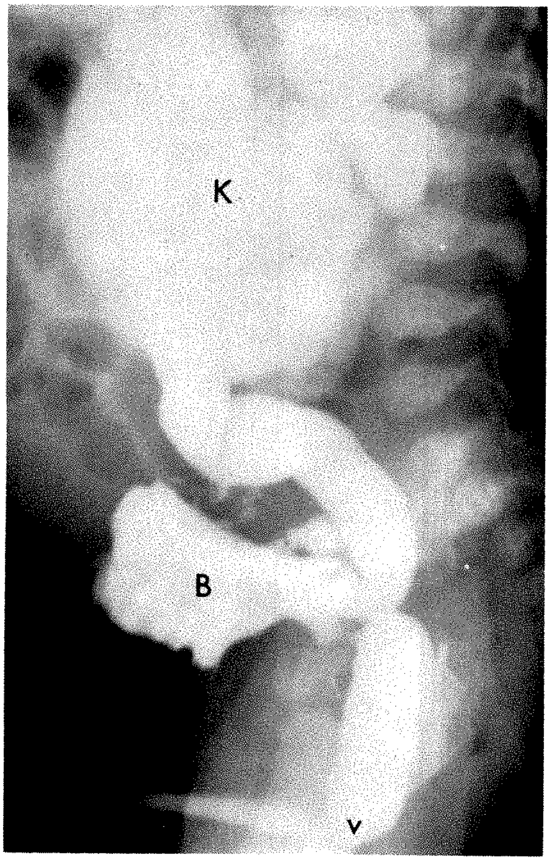

Fig. 7. Bilateral hydronephrosis due to posterior urethral valves. This lateral retrograde cystogram shows the greatly distorted kidneys (K), free ureteral reflux, the trabeculated bladder (B), and the valves themselves (V) sagging well into the membranous urethra. The masses were found, at the age of 27 days, during investigation of failure to thrive.

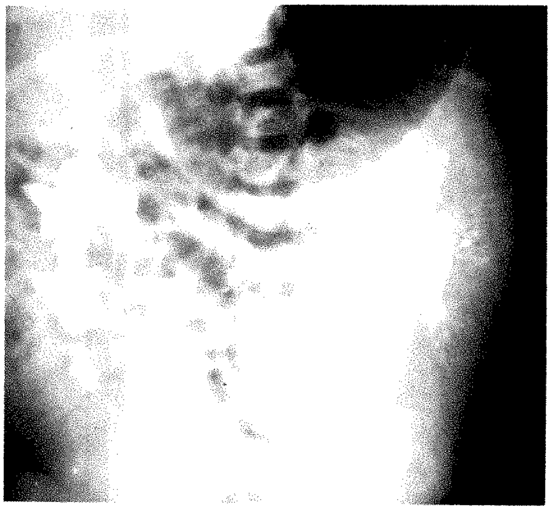

Fig. 8. Polycystic kidneys shown on a retrograde pyelogram at the age of 7 days but never biopsied. Renal enlargement and pelvicalyceal distortion are evident. Reflux into the tubules shows dilatation and distortion of those structures, and this appears to represent the renal tubular ectasia form of polycystic disease. Now 12 years old, the child is hypertensive and has diminished renal function.

Two of these newborns came to autopsy in early infancy, and both showed cystic disease of other abdominal viscera as well as of the kidneys. The diagnosis in the other 5 cases rests on the physical examination, pyelographic findings, family history, and course, with increasing renal decompensation developing in several.

WILMS' TUMOR

Except for their relative infrequency, Wilms' tumors of the newborn do not seem to be diagnostically different from Wilms' tumors in older children. Four of the 5 cases were found during the first 2 days of life. Intravenous urograms showed that the mass was intrarenal in 4 cases, and in the fifth case the involved kidney showed no pyelographic function. No metastases were found. One child died in the preoperative period, 1 died unexpectedly at home a few weeks after the apparently total removal of his tumor, 2 are well 5½ and 6½ years after tumor excision and radiation therapy, and 1 was operated on only a few months ago but apparently is well. The relatively favorable prognosis of Wilms' tumors found during the first year of life is well known.[12]

MALPLACED KIDNEY

Renal ectopia accounted for 4 abdominal masses. There were 1 case of single presacral kidney, 1 case of single kidney lying low in the flank, and 2 cases of crossed ectopy. These "masses" often felt like kidneys to experienced clinicians. Pyelography made the diagnosis obvious. Two of the 4 cases had serious associated congenital anomalies.

One of the 25 cases of multicystic dysplastic kidney involved half of a horseshoe kidney.

OTHER RENAL MASSES

There was 1 case of renal vein thrombosis. The infant developed hematuria and a flank mass on the first day of life. The affected kidney did not function on urography and was large, although not large enough to show a clear nonopacification effect. The major diagnostic clue was the maternal diabetes. The infarcted kidney was removed, and the child has been doing well.

One renal mass was difficult to classify pathologically but was finally diagnosed as a benign cystic hamartoma of the kidney.

INTESTINAL DUPLICATION

The 11 duplications (enteric cysts)[8] (Fig. 9, *A* and *B*) arose from various sites from the duodenum to the cecum, the neighborhood of the ileocecal junction being a favorite locus. One duplication originated in the retroperitoneum but had ballooned into the abdominal cavity. Although all of these cases turned up during the first 3 weeks of life, only 3 were found immediately after delivery. Eight patients presented with complete or partial intestinal obstruction, including 2 cases complicated by volvulus and 1 by cecocolic intussusception. The palpable masses were usually round but sometimes tubular. They were often mobile. A mobile elongated mass stretching across the abdomen is likely to be a duplication. Except for 1 child with

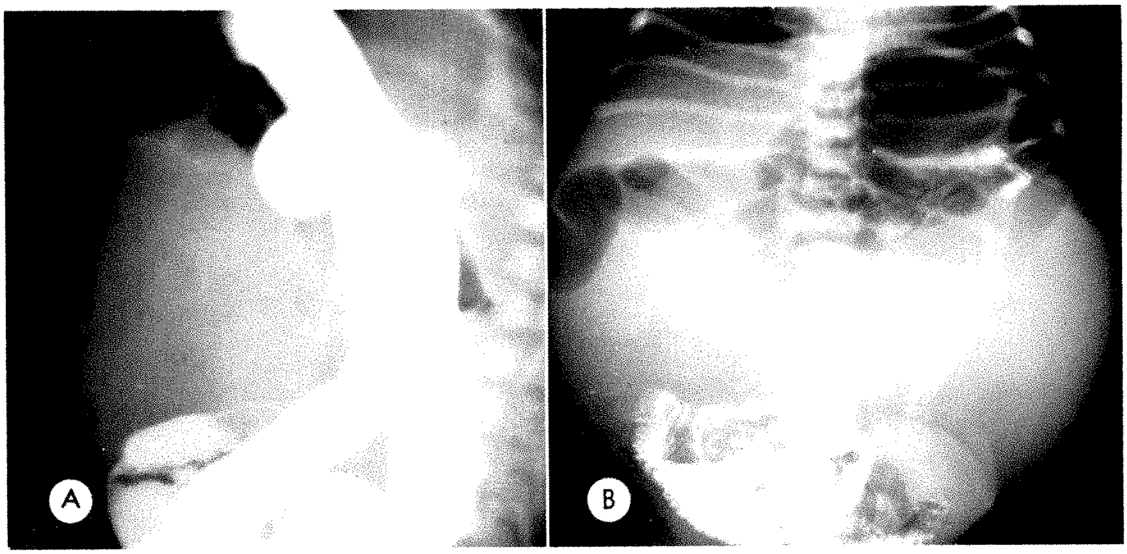

Fig. 9. (*A* and *B*) Jejunal duplication. These lateral and postevacuation anteroposterior barium enema roentgenograms show a long mass, found at birth, lying anterior to the transverse colon and descending colon and above the hepatic flexure.

hip dislocation, no other congenital abnormalities were found.

Plain roentgenograms showed obstruction, when present, and the mass, when it was larger than about 3 cm. in diameter. Its extrarenal and intra-abdominal position was readily evident on urography. The total body opacification effect was only occasionally seen, probably because the masses were seldom large enough and were surrounded by obscuring bowel gas. The diagnosis of duplication can be strongly suggested in the presence of a mass that is discrete and mobile by palpation, a sharply outlined intraperitoneal mass on the roentgenograms, and intestinal obstruction.

These duplications were promptly removed. One boy developed a fecal fistula after surgery; all the others did entirely well.

OTHER GASTROINTESTINAL MASSES

One malrotation with volvulus and infarction presented clinically as a cystic mass and roentgenologically as a minimally nonopacifying lesion. Another case of infarcted intrauterine volvulus presented as a densely calcified mass with duodenal obstruction.[11] One case of meconium ileus with intrauterine perforation, peritonitis, and obstructing adhesions presented as a low abdominal mass; roentgenograms showed peritoneal calcification around a 7 cm. mass, which was ileum filled with meconium. The second case of meconium ileus caused a massive volvulus, which on urograms had shown as a nonopacifying septated mass.

An enormous omental cyst, very soft and quite difficult to outline by palpation, was clearly shown on urograms both by the total body opacification effect and by bowel gas displacement. The only neonatal cyst of the mesentery was obscured by overlying bowel on the plain roentgenograms, and urography was not performed. An annular obstructing leiomyosarcoma of the transverse colon was found at the age of 10 days; the patient is well 9 years after surgery. One mass turned out to be cystic dilatation of intestine, with intrauterine perforation and calcific peritonitis, proximal to ileal atresia; the nonopacification of this mass was striking.[18] In all of these newborns, the referring physicians had suspected the presence of cystic or solid tumors.

HYDROCOLPOS, HYDROMETRA

Hydrocolpos[23] is massive distention of the vagina, and hydrometra is massive distention of the uterus. The two conditions (Fig. 10, *A* and *B;* and 11, *A* and *B*) are often associated. The distention is caused by blockage of the genital tract by stenosis of the uterine cervix, vaginal stenosis or diaphragm, or hymenal imperforation, with accumulation of secretions.

All 9 cases were found on the first day of life. Three were relatively simple, with obstruction of the genital tract by cervical atresia, vaginal stenosis, and hymenal imperforation, respectively. A urachal cyst in 1 case and supernumerary digits in another were the only other congenital deformities in these 3 baby girls. In each case a fixed anterior midline suprapubic mass could be palpated. Simultaneous opacification of the bladder and rectum readily showed that the mass lay in between. The imperforate hymen was cured by incision. The other obstructions were repaired; the patients are doing well but are not yet pubertal.

The other 6 cases were much more complex. Five had imperforate ani, and 4 had rectovaginal or rectouterine fistulae. The external genitalia were often abnormal. The sex of the child was in doubt in 3 cases. One newborn apparently was a true hermaphrodite and is a mature male 17 years after removal of a fallopian tube, parovarian tissue and a massively distended uterus and vagina; gonadal biopsy later showed testicular tissue. In several of these cases, roentgenograms showed air from the rectal fistulae within the fixed midline anterior suprapubic masses. Roentgenograms obtained by opacifying the bladder and the genital tract often showed the anatomy clearly.

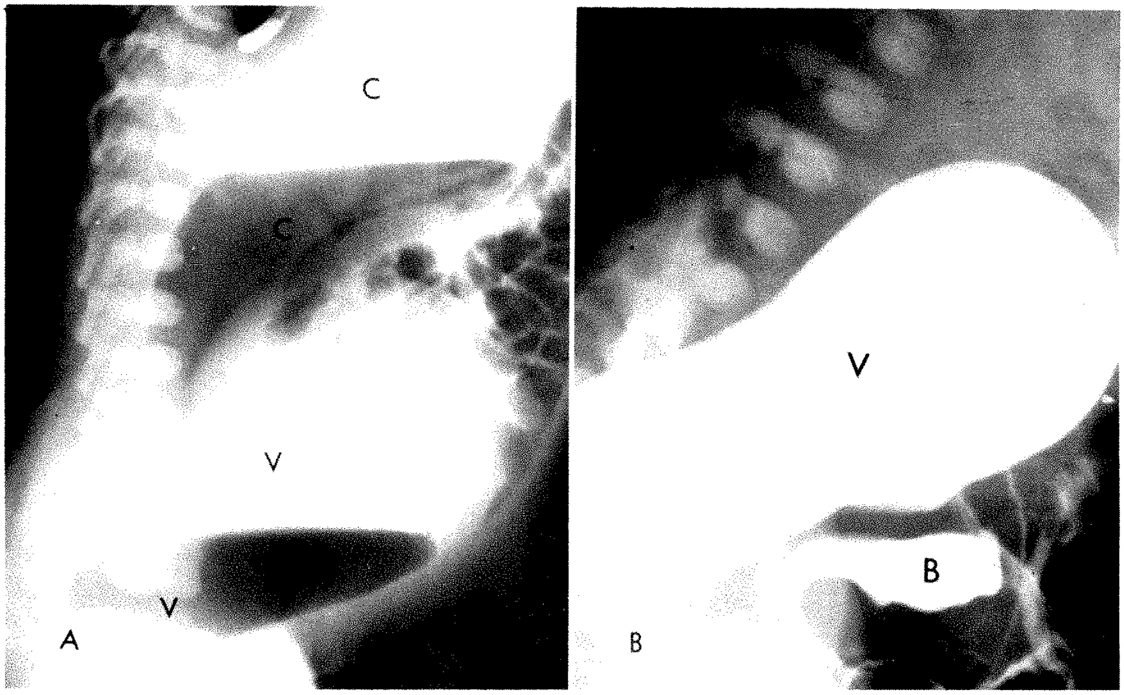

Fig. 10. (*A* and *B*) Hydrometrocolpos, with vaginal stenosis, imperforate anus, rectovaginal fistula, and partial exstrophy of the bladder. The preliminary inverted lateral roentgenogram (*A*) shows air and fluid within the obstructed colon (C) and vagina (V). (*B*) The examination performed after a decompressing colostomy shows the enormous vagina (V) behind the bladder (B).

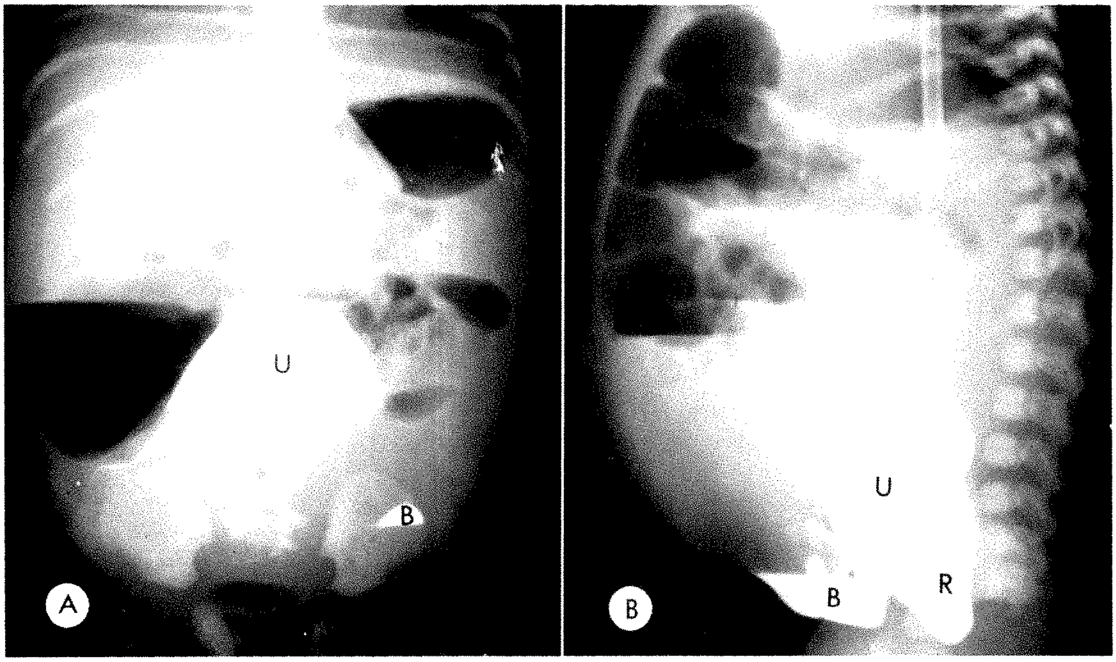

Fig. 11. (*A* and *B*) Hydrometra of half of a bicornuate uterus, with imperforate anus, rectogenitovesical fistula and sacral hypoplasia. These inverted anteroposterior and erect lateral roentgenograms, taken after opacification via the cloacal sinus, show the obstructed rectum (R), distended uterus (U), and bladder (B).

Three of these patients died early in life, and the other 3 have required repeated operations upon the genitourinary tract.

OVARIAN CYST

Six newborns had ovarian or parovarian cysts[5] (Fig. 12), 1 case being bilateral. All of these masses were found during the first 2 days of life. Several were large enough to extend across the midline and into the upper abdomen, and several developed fairly long pedicles. In no case were there associated congenital anomalies.

Plain roentgenograms generally showed the mass quite clearly. Usually, it appeared to be more abdominal than pelvic. In 2 cases there was slight obstruction of one lower ureter. Except for 1 cyst measuring only 2.5 cm. in diameter, all of these masses showed the total body opacification effect and thus were demonstrably avascular.

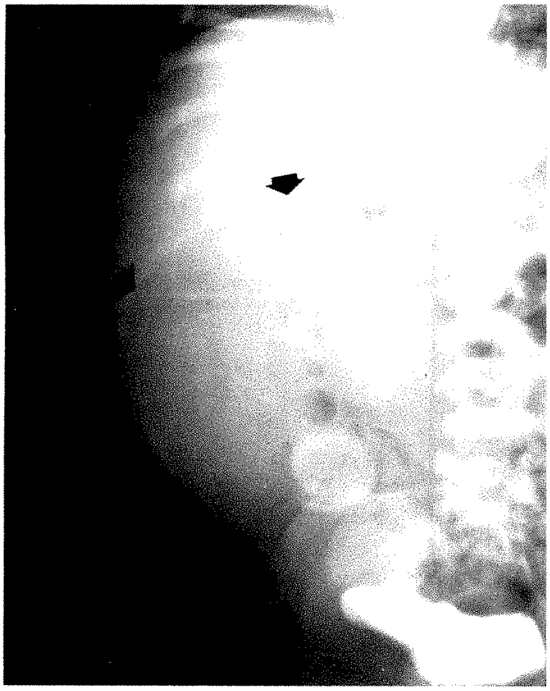

FIG. 12. Right parovarian cyst arising from the epioophoron, a wolffian duct remnant. This 20 minute urogram shows a large mass next to but distinguishable from the liver by its homogeneous nonopacification. The round density below the right kidney is the umbilicus. The mass was found on the first day of life.

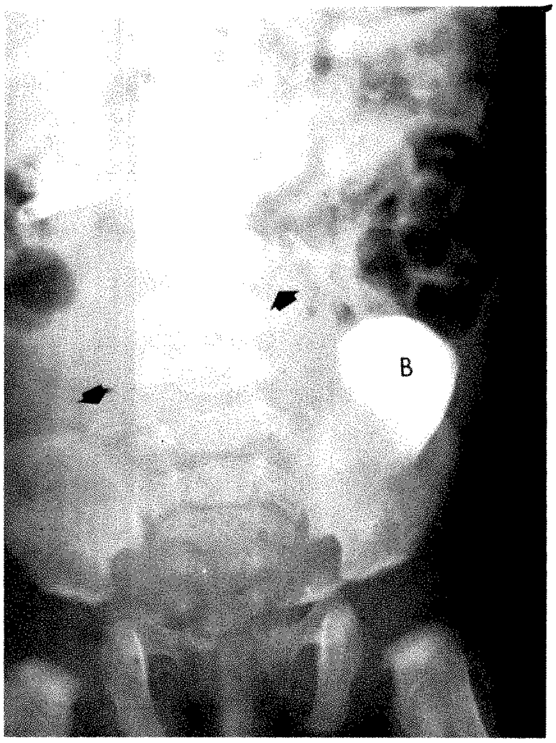

FIG. 13. Low retroperitoneal neuroblastoma. The arrows mark tumor calcification. The right ureter is pushed across the midline at the level of L 2, and the bladder (B) is strikingly displaced. The mass was found at the age of 3 days.

All of these cysts were removed uneventfully.

HEPATOBILIARY MASSES

Two solitary liver cysts (Fig. 1, *A* and *B*), 1 choledochal cyst, 1 infected hydropic gallbladder, and 1 hepatoma[3] presented during the newborn period. The choledochal cyst and one of the cases of solitary liver cyst afforded striking examples of the total body opacification effect. The hepatoma was enormous and partially calcified. None of these newborns had any associated congenital malformations.

NEUROBLASTOMA

There were 9 cases of neuroblastoma (Fig. 13 and 14). Four arose in an adrenal, but 5 originated in the retroperitoneum below the kidney, apparently either from the lower part of the urogenital ridge or from the organ of Zuckerkandl. This con-

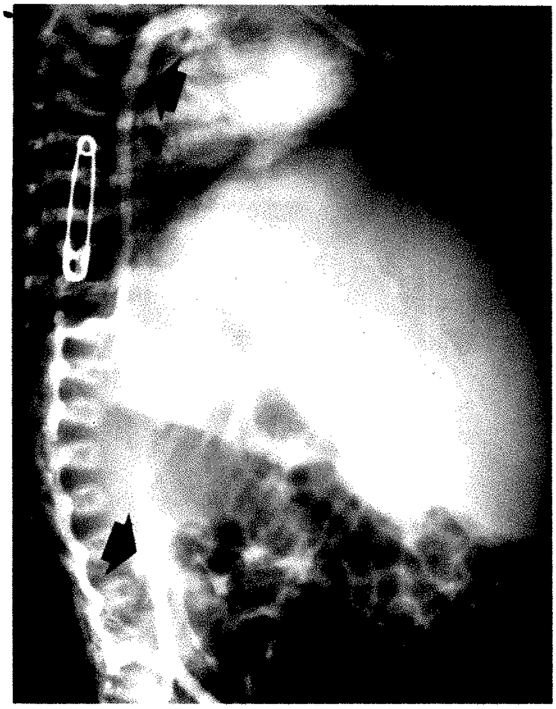

FIG. 14. Neuroblastoma. This lateral study of the inferior vena cava shows that it is obstructed (lower arrow). Blood reaches the heart via the vertebral plexus of Batson and the azygos vein (upper arrow). Hepatomegaly and an abdominal mass were noted at birth.

trasts with abdominal neuroblastomas in older children, most of which arise in an adrenal. Five of these masses were found during the first day of life. In 3 cases the liver, enlarged by metastases, overshadowed the primary tumor. Some of the masses were nodular, and all were firm or stony hard. No bony or pulmonary metastases were found. None of these infants had any other congenital disease.

Roentgenograms showed tumor calcium in 3 cases. Venography showed obstruction of the inferior vena cava in 1 newborn (Fig. 14). Apart from 1 instance of secondary hydronephrosis, the kidneys were intrinsically normal. The neuroblastomas arising in an adrenal depressed and rotated the adjacent kidneys. Upward, forward and lateral renal displacement was effected by the lower retroperitoneal primary tumors, however, which also often displaced the ureters and bladder to a startling degree (Fig. 13).

These infants were treated hopefully and aggressively by means of surgery, radiation therapy, and chemotherapy. Three have died. The other 6 are in good health. Four patients are alive and well 1 year, $2\frac{1}{2}$ years, 3 years, and $3\frac{1}{2}$ years after biopsy proof of hepatic metastases. These children again demonstrate the relatively hopeful prognosis carried by neuroblastomas, even when metastatic to the liver, found early in infancy.[5]

ABSCESS

Four abscesses presented as abdominal masses, all after the age of 1 week. One, around the left kidney and in the left lateral retroperitoneum, was associated with generalized sepsis. The others—2 in the pelvis and 1 in the right flank—probably were extensions from omphalitis.

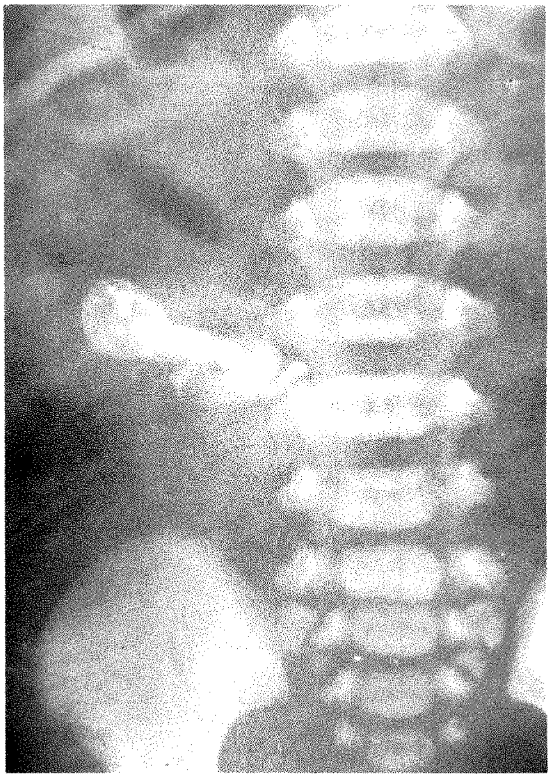

FIG. 15. Bony structures within a retroperitoneal teratoma, found at the age of 2 days.

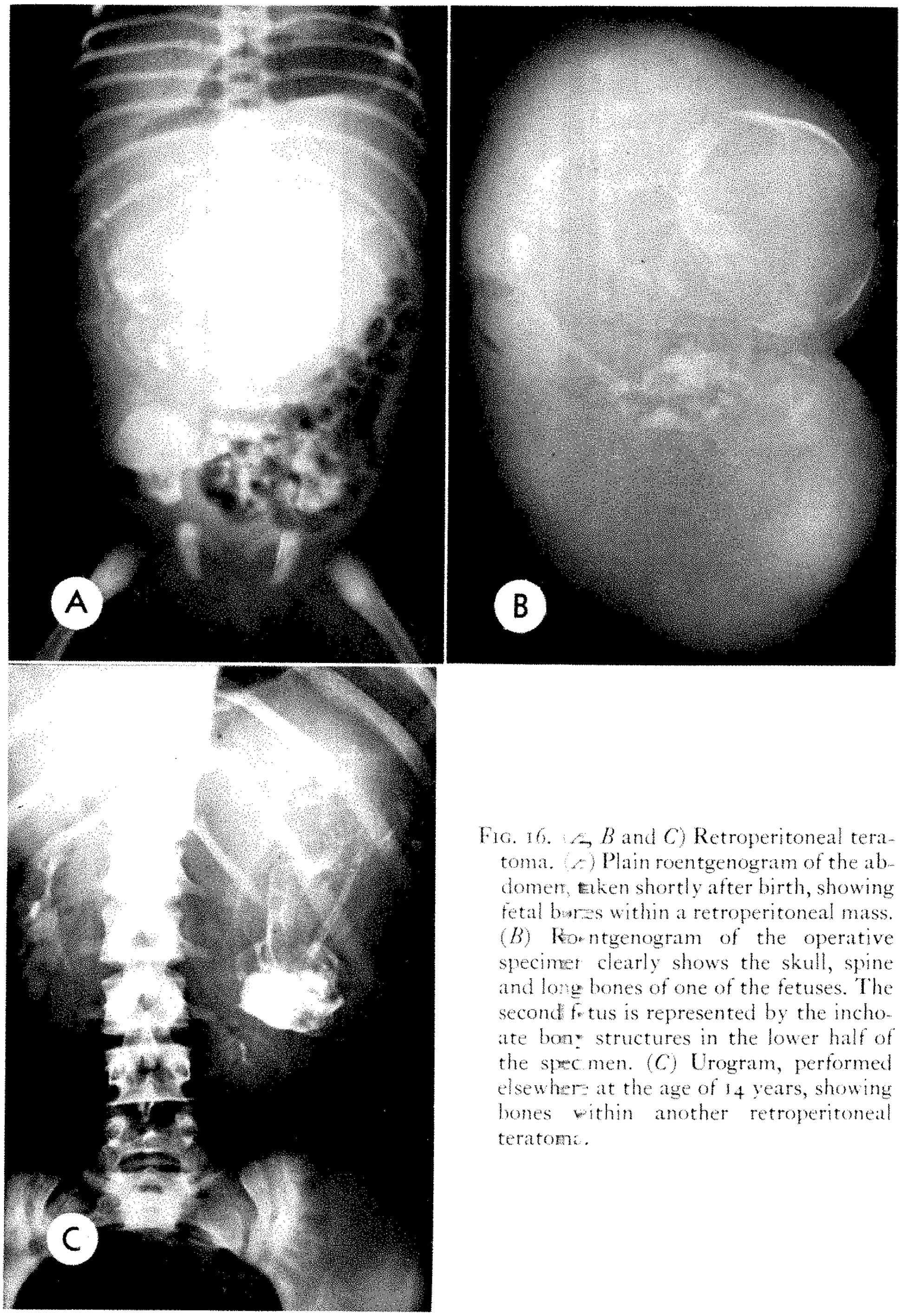

Fig. 16. (A, B and C) Retroperitoneal teratoma. (A) Plain roentgenogram of the abdomen, taken shortly after birth, showing fetal bones within a retroperitoneal mass. (B) Roentgenogram of the operative specimen clearly shows the skull, spine and long bones of one of the fetuses. The second fetus is represented by the inchoate bony structures in the lower half of the specimen. (C) Urogram, performed elsewhere at the age of 14 years, showing bones within another retroperitoneal teratoma.

None of the abscesses appeared to originate in the appendix. The roentgenographic signs varied with the location, and included thickening of the abdominal wall, renal and ureteral displacement, colonic obstruction and displacement, pockets of abscess gas, and obliteration of the fat planes of the abdominal wall. The effacement of the fat planes by local inflammation was slightly enhanced by the total body opacification effect, which (because of fat's relatively poor blood supply) increased fatty contrast elsewhere but not in the inflamed hypervascular areas. Two of these infants (one with significant congenital heart disease) succumbed; the other 2 are well.

TERATOMA

Two of these 117 abdominal masses were retroperitoneal teratomas[19] (Fig. 15; and 16, *A*, *B* and *C*). Most neonatal teratomas present as obvious buttock masses,[6] but 1 of the present cases had neither pelvic nor gluteal component, and only a small part of the other extended down into the presacral fossa.

Roentgenograms of these 2 newborns showed that the retroperitoneal tumors contained bony structures; in 1 of them skull bones, vertebrae, and extremity bones could be identified. In that case,[7] a 1 day old girl, the operative specimen consisted of fetal membranes, two partially formed fetuses, and two rudimentary umbilical cords. That patient has recently had another retroperitoneal teratoma excised elsewhere, at the age of 14 years (Fig. 16, *A*, *B* and *C*). The other case has done entirely well. Neither girl had congenital disease elsewhere.

SUMMARY

A review of 117 abdominal masses found in the first 4 weeks of life shows that more than half were renal. Multicystic kidney disease was the most common diagnosis. Hydronephrosis, intestinal duplication, hydrometra or hydrocolpos, neuroblastoma, polycystic kidney disease, and ovarian cyst followed in frequency. Fewer than 15 per cent of the masses were malignant. The clinical data in brief and the details of the roentgenographic findings are given. Use of good roentgenographic technique plus an appreciation of the principle of total body opacification will enable one to select the proper diagnosis from the many possibilities surprisingly often. Surgery permanently cured 60 per cent of these newborns. Only one-fifth of the present series died soon after birth. Even malignant masses often responded well to therapy.

In short, this material indicates that a vigorous and hopeful diagnostic and therapeutic approach is fully warranted when an abdominal mass is found in a newborn.

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ROENTGENOGRAPHIC ESTIMATION OF KIDNEY SIZE IN NORMAL INDIVIDUALS WITH EMPHASIS ON CHILDREN*

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THE size of kidneys as measured in frontal roentgenograms of the abdomen in normal living adults has been investigated by several authors.[1,2,4–11] The mean values for kidney length in the various series ranged from 11.1 to 13.7 cm., with values for one standard deviation varying between 0.66 and 1.29 cm. The values for kidney width ranged from 5.1 to 6.6 cm., with values for one standard deviation varying between 0.37 and 0.79 cm. The reported values for kidney surface area were as follows: in the series in which the surface area was determined by means of a planimeter or by a special formula ($\pi \times$ kidney length $\times$ kidney width/4), the values ranged from 47.7 to 68.5 cm.^{2}, with values for one standard deviation varying between 5.3 and 7.77 cm.^{2}; when determined by simply multiplying kidney length by kidney width, the kidney surface area varied from 69.1 to 84.3 cm.^{2}, with values for one standard deviation varying between 7.31 and 15.4 cm.^{2}. Kidney length, width, and surface area were greater in men than in women, and in most series they were greater on the left side than on the right side in both sexes.

The kidney size of normal living children was measured in roentgenograms of the abdomen by Hodson *et al.*[3] These authors have investigated the kidney length, and the kidney surface area by means of a planimeter in 393 children from 0 to 16 years of age. The values obtained for kidney length, plotted against age, were given by the authors in a graph which has been redrawn in Figure 1. There was no difference in renal size between boys and girls. A difference in length up to 0.5 cm. between the two kidneys was not infrequent.

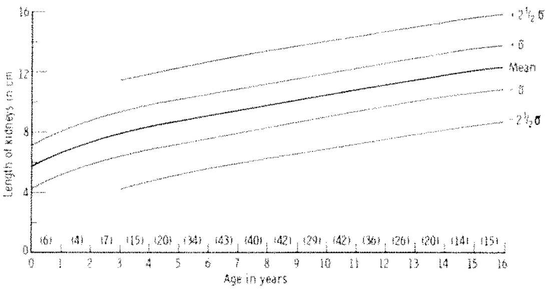

FIG. 1. Graph of kidney length plotted against age in children (redrawn from Hodson, C. J., Drewe, J. A., Karn, M. N., and King, A. *Arch. Dis. Childhood*[3]).

PRESENT INVESTIGATION IN CHILDREN

The present study, undertaken in an attempt to determine a simpler way to estimate the size of normal kidney in children which could be used in routine work, is based on a review of excretory urograms of 50 children from 0 to 14 years. Males and females were represented in nearly equal number. All children had no evidence of urinary tract disease either clinically or roentgenographically. The kidney length could be measured on the right side in 50 patients, and on the left side in 45. The kidney width could be measured on the right side in 49 and on the left side in 45 patients.

KIDNEY LENGTH

The values for kidney length in the 95 kidneys were first plotted against age and the results were then superimposed on Hodson's graph for kidney length, as shown in Figure 2; as is apparent from

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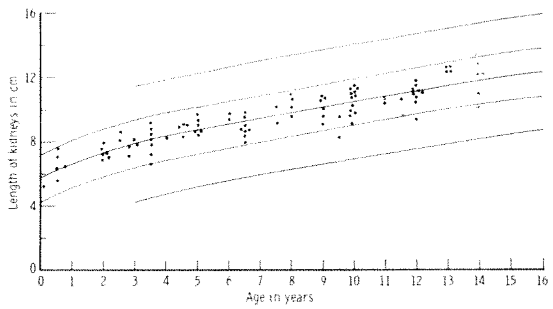

Fig. 2. Author's graph of kidney length plotted against age in children, superimposed on the graph obtained by Hodson *et al.* (as shown in Figure 1).

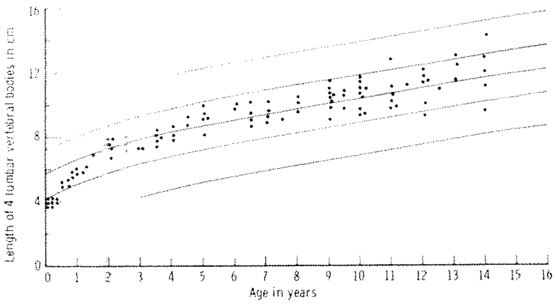

Fig. 4. Author's graph of the length of the comparative lumbar spine segment, as measured by the method shown in Figure 3, superimposed on the graph for kidney length of Hodson *et al.*

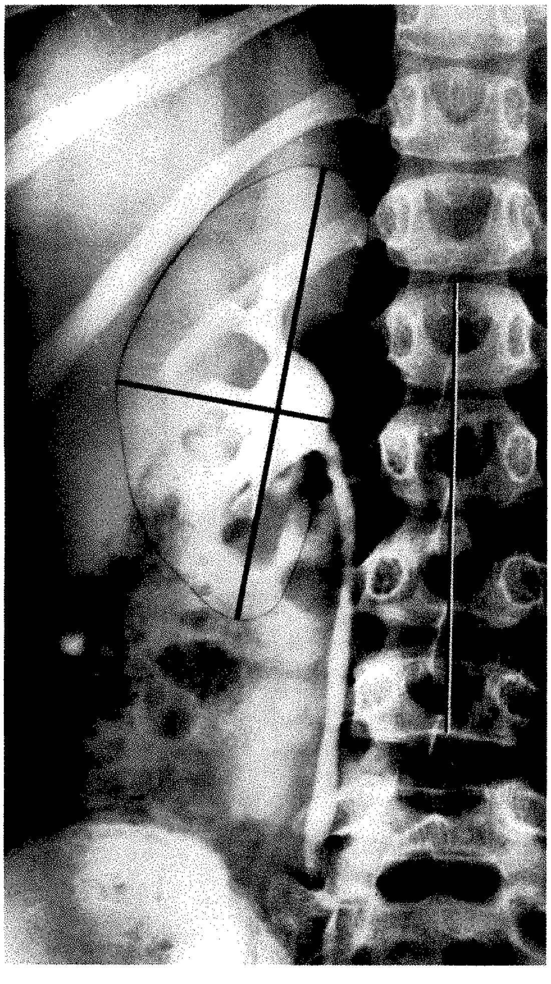

Fig. 3. Comparative measurement of the length of the kidney and the length of a segment of the lumbar spine, comprising the 4 upper lumbar vertebral bodies and the 3 intervertebral spaces between them.

this figure, the values obtained in our series confirm the results obtained by Hodson *et al.*

The length was then measured of the first 4 lumbar vertebral bodies including the 3 intervertebral spaces comprised by them, as shown in Figure 3, in the same 50 children as well as in an additional 50 "normal" unselected children from 0 to 14 years of age. The values obtained were again plotted against age and the results were then superimposed on Hodson's graph for kidney length, as shown in Figure 4. As is apparent from this figure, the length of this segment of the lumbar spine corresponded to the normal length of the kidney (±1 cm.) throughout childhood, with the exception of the first 1–1½ years of life in which the length of a normal kidney was greater.

Contrary to the findings reported in adults but in keeping with the results obtained in children by Hodson *et al.*, there was no significant difference in kidney size between males and females in this series. Among 44 patients in whom both kidneys could be measured, the left kidney was longer than the right in 28, the right was longer than the left in 10, and the two kidneys were equal in length in 6 children. As in adults, the left kidney was often larger than the right. In our series the difference between the two kidneys was greater than that given by Hodson *et al.*, having the following distribution:

Difference in length in mm. between the two kidneys :	1	2	3	4	5	6	7	8	9	10
No. of children :	3	2	4	3	12	4	3	3	2	2

KIDNEY WIDTH

The maximal width of 94 kidneys was measured as shown in Figure 3. The width of each kidney was then plotted against its height and the ratio between these two measurements was determined; expressed in percentage, the values obtained were as follows:

Kidney width in % of kidney length :	40–45	46–50	51–55	56–60	61–65
No. of kidneys :	8	26	35	18	7

These figures indicate that in the majority of cases the width of a normal kidney is 45–60 per cent of its length.

CONCLUSIONS AND SUMMARY

The results of previous investigations dealing with renal size in normal living adults and children, as measured in roentgenograms of the abdomen are summarized. The present study, based on a small series of "normal" children from 0 to 14 years of age, suggests that the average kidney length corresponds very closely to the length of the first 4 lumbar vertebral bodies throughout childhood, with the exception of the first 1–1½ years of life when the length of the normal kidney is greater than that of this segment of spine. The width of a normal kidney in most children corresponds to 45–60 per cent of the kidney length. A difference in length of the two kidneys up to 1 cm. can occur normally.

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ARTERIOGRAPHIC DEMONSTRATION OF PERIRENAL HEMATOMA AND WILMS' TUMOR IN A HYPERTENSIVE CHILD*

A CASE REPORT

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ALTHOUGH perirenal hematomas were purportedly described in the medical literature as early as 1700,[13] the preoperative or antemortem diagnosis of such lesions, until recently, often remained an enigma. The number of these cases associated with hypertension is astonishingly small.[4] Presented below is a case of a hypertensive child in whom perirenal hematoma and Wilms' tumor were arteriographically demonstrated.

REPORT OF A CASE

A left flank mass was discovered in an asymptomatic 8 month old boy on a routine examination. Subsequently, he had a nephrectomy with excision of a Wilms' tumor and postoperatively he received radiation therapy and actinomycin D. No metastatic foci were in evidence at that time. Aside from poor weight gain, he did well until the age of 2½ years (18 months later) when a right flank mass was discovered. Three weeks after its detection, it suddenly increased in size and the child was transferred to the Children's Hospital Medical Center for further evaluation and treatment.

Physical examination on admission revealed a pale, diaphoretic child, in moderate respiratory distress, who appeared acutely ill. His temperature was 99° F., pulse 180, and respirations 36. His blood pressure was 140/60 and shortly after admission rose to 170/110. No papilledema was present. Shotty lymph nodes were palpable in the anterior and posterior cervical chain. There was minimal retraction of the chest and decreased breath sounds were audible over the right lung base, posteriorly. The heart was not enlarged; a Grade II, systolic, ejection murmur was heard low along the left sternal border. The abdomen was distended by a firm mass which filled the right upper quadrant and extended to the right iliac crest. The clinical impression was that the patient had hepatic metastasis from his previously resected tumor.

The urine had a specific gravity of 1.015 and a pH of 6.0; 5 mg. per cent of albumin was present and the sediment contained 50 red blood cells and 5 white blood cells per high power field. The hemoglobin was 7.9 gm., the white blood cell count was 18,100 with a normal differential, and the platelets were 698,000 per cu. mm. The nonprotein nitrogen was 20 mg. per cent, the bilirubin, alkaline phosphatase, and serum proteins were normal. The sodium was 147 mEq., the potassium 4.4 mEq., the chloride 101 mEq., and the CO_2 14.9 mEq. per liter. Bone marrow examination was within normal limits. An electrocardiogram revealed sinus tachycardia but was otherwise normal. Blood cultures were taken when the fever increased, but were negative. Vanillyl mandelic acid (V.M.A.) excretion was 1.7 mg. per 24 hours and catecholamine determination was 10 μg. per 24 hours (both normal).

Roentgenograms of the chest showed a normal heart and lungs with no evidence of metastasis or pleural effusion. The right hemidiaphragm was elevated by a homogeneously dense abdominal mass (Fig. 1*A*). Skeletal survey showed scoliosis, judged to be one of the sequelae of previous irradiation,[10] but otherwise no abnormalities. Intravenous pyelograms (Fig. 1*B*) demonstrated the right upper quadrant mass to be a pyelocaliectatic kidney rather than an enlarged liver as had been clinically suspected.

Transfemoral retrograde aortography was performed after arteriotomy and passage of a radiopaque catheter to the level of the renal artery under image intensification fluoroscopy. Serial films (Fig. 2, *A*, *B* and *C*) exposed during injection demonstrated a patent, but attenuated, renal artery which was tented cephalad in its midportion by an enlarged capsular artery. The latter extended around the periphery of the mass and kidney and communicated with tortuous, large vessels which resulted in tumor stain. The nephrogram phase demonstrated a perirenal unopacified rim which was interpreted as representing subcapsular hematoma or tumor infiltrate.

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An inferior vena cavagram (Fig. 3) made immediately thereafter demonstrated the vena cava to be compressed and displaced medially by the renal mass. Retrograde pyelography revealed a partially obstructed ureteropelvic junction, but normal urine flow was obtained after passage of the catheter tip into the renal pelvis.

Throughout his hospital course, hypertension (up to 180/120) persisted despite a vigorous antihypertensive medical regimen. The patient was treated with orthovoltage local irradiation to the tumorous kidney (1,284 roentgens) and systemic cancer chemotherapy (actinomycin D and vincristine), but the mass did not change appreciably in size. On the nineteenth hospital day, icterus suddenly became manifest and the blood pressure fell in spite of transfusions and vasopressors. Shortly thereafter, the patient became unresponsive, cyanotic, and expired.

At autopsy, the abdomen was found to be protuberant and the abdominal skin stretched and shiny. The peritoneal cavity contained 180 cc. of clear, golden fluid and a scanty fibrinous exudate. The liver was not enlarged and presented no gross evidence of bile stasis. It was displaced ventrally by a 12 cm. in diameter, dark red, globular mass, which was enclosed by the perirenal capsule, and extended over the anterior surface of the kidney. The wall of the mass was generally firm and up to 0.8 cm. thick, but focally it was soft and friable. Grossly, its contents appeared to be composed of partly clotted blood and necrotic debris. The kidney was visible from the posterior aspect only (Fig. 4). and measured 11 cm. in vertical axis. The renal parenchyma was unduly soft and multiple punctate and linear areas of

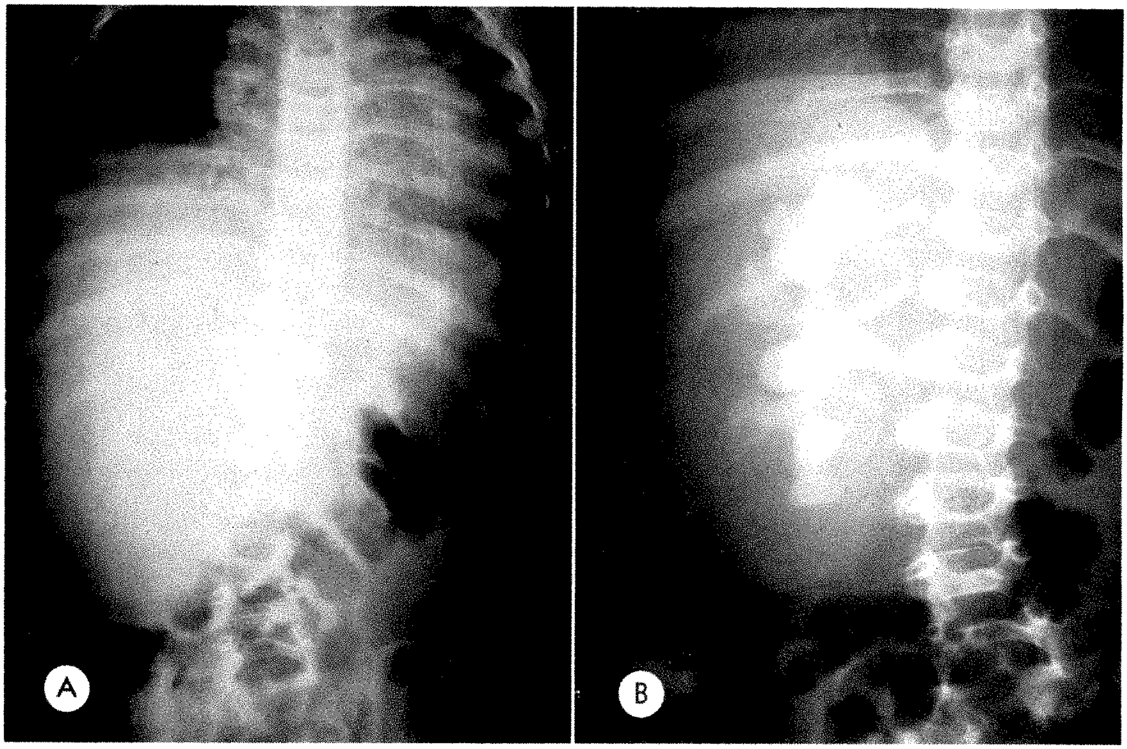

FIG. 1. (*A*) Anteroposterior roentgenogram of the abdomen demonstrating the large abdominal mass inseparable from the liver. The diaphragms are elevated and the bowel is displaced. (*B*) Intravenous pyelogram demonstrates pyelocaliectasis.

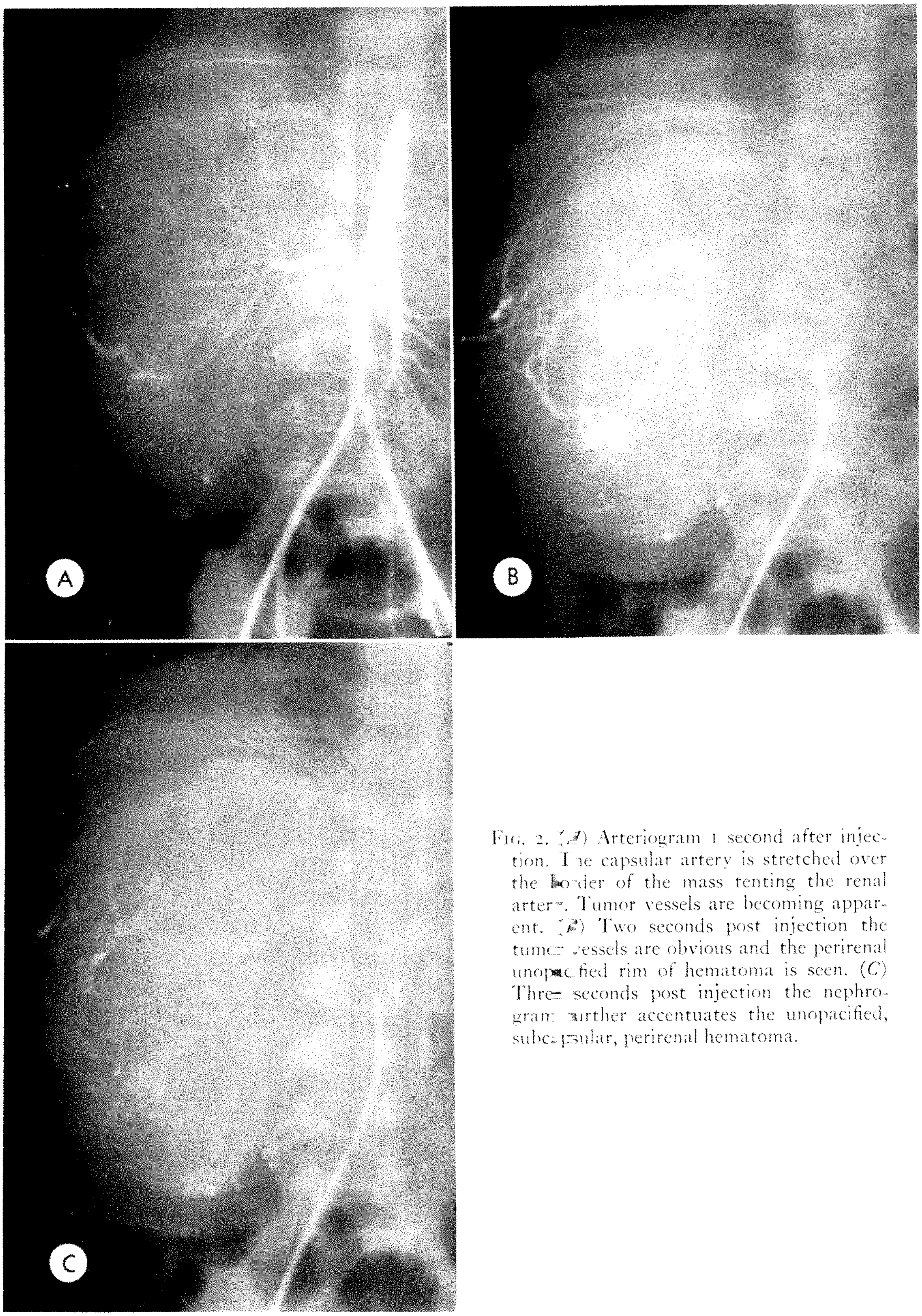

Fig. 2. (*A*) Arteriogram 1 second after injection. The capsular artery is stretched over the border of the mass tenting the renal artery. Tumor vessels are becoming apparent. (*B*) Two seconds post injection the tumor vessels are obvious and the perirenal unopacified rim of hematoma is seen. (*C*) Three seconds post injection the nephrogram further accentuates the unopacified, subcapsular, perirenal hematoma.

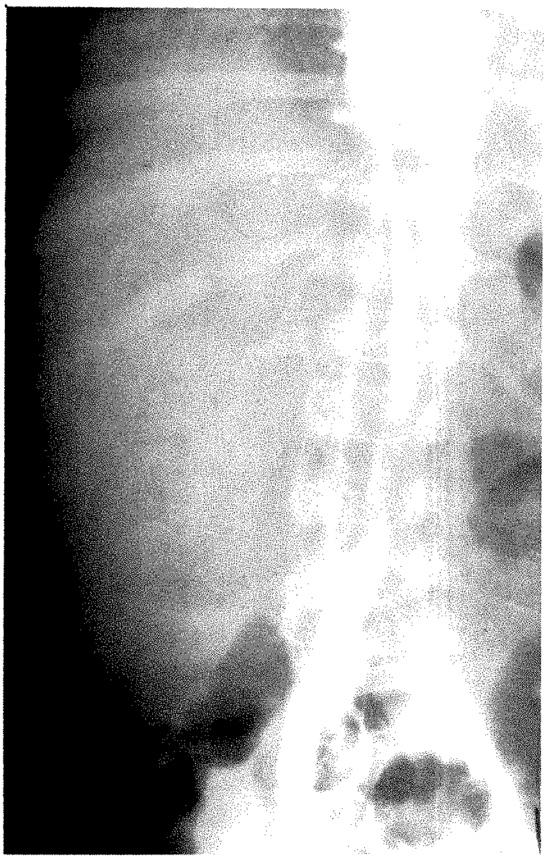

FIG. 3. The inferior vena cavagram demonstrates compression and medial displacement of the inferior vena cava.

granular necrosis were seen in the cortex.

Two tumor nodules were identified within the kidney: one near the superior margin of the hilus and a second, focally hemorrhagic, peripheral nodule near the inferior pole. The latter nodule blended imperceptibly with the surrounding tissue and extended to the cortical surface. The attenuated renal artery and vein were patent but displaced as demonstrated on the arteriogram. The inferior vena cava was compressed as it arched over the posteromedial aspect of the kidney and mass. The ureter was displaced medially and the renal pelvis was dilated.

Microscopically, the two intrarenal tumor nodules were composed of malignant mesodermal elements including undifferentiated embryonal cells and rhabdomyoblasts. In addition, the tumor contained foci of epithelial tubular formation, nests of transitional-like cells, rare glomeruloid bodies and extensive fibrosis. The material within the perirenal mass was markedly necrotic and consisted principally of blood. Among the necrotic debris, however, cellular structures could be discerned; these were tubular entities and spindle cells, unlike the fibroblasts seen in an organizing thrombus. Among the necrotic material, vestiges of a few moderately large vessels were identified and incorporated within the fibrous walled capsule were a few arterioles and venules.

Widely disseminated foci of sepsis were present in the heart, lungs, and thymus as well as within the perirenal hematoma. The kidney manifested areas of tubular necrosis and abscess formation. *Staphylococcus aureus* was common to all sites cultured and *Escherichia coli* was cultured from the kidney.

In summary, the autopsy revealed a hemorrhagic Wilms' tumor nodule in continuity with

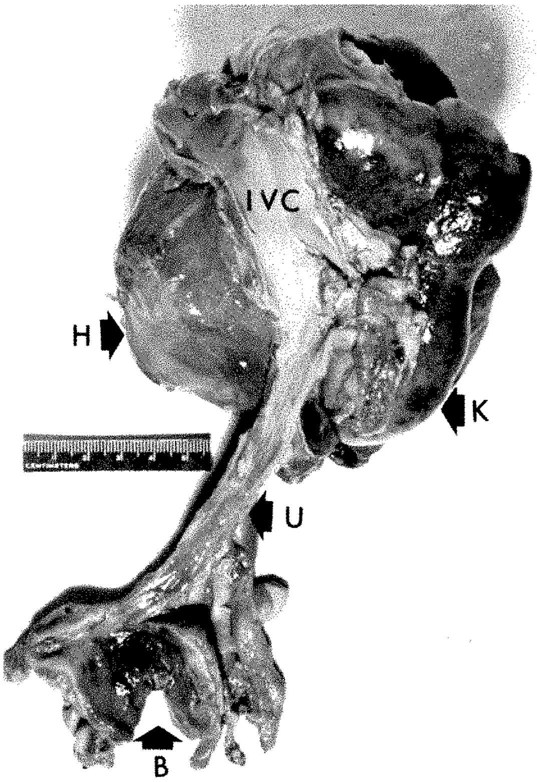

FIG. 4. Photograph of pathologic specimen, posterior view. The hematoma is anterior to the kidney, vessels and ureter. (K—kidney, H—hematoma, IVC—inferior vena cava, U—ureter, B—urinary bladder.)

a subcapsular perirenal mass. The latter, although necrotic, contained within it cellular elements entirely compatible with the diagnosis of extrarenal tumor growth with ensuing hemorrhage or infarction. Alterations secondary to the perirenal mass included displacement and partial compression of the ureter with resultant hydroureter, hydronephrosis, and acute pyelonephritis. Since no extrarenal metastatic foci were identified, it is assumed that the Wilms' tumor arose *de novo* rather than as a metastatic deposit from the original tumor in the previously resected contralateral kidney.

DISCUSSION

As with any rapidly growing neoplasm, the blood supply in Wilms' tumor is soon outstripped and necrosis ensues. In these necrotic areas, it is not unusual to find tumor invading blood vessels and subsequent small, localized areas of hemorrhage.[9] Occasionally, with massive hemorrhage there is extracapsular extension into the retroperitoneal space. The unique pathologic features in the case presented include the large size of the hemorrhage, its confinement to the subcapsular space, its impingement on the renal artery, and its role in the causation of partial ureteropelvic obstruction.

It is of interest to speculate on the relationship of the perirenal hematoma to the patient's hypertension. Had this patient survived, the subcapcular hematoma might have undergone resorption with resultant amelioration of the hypertension.[14] On the other hand, it is more likely that the organizing hematoma might have produced a firm, perirenal hull as has been experimentally demonstrated by Page[12] and has subsequently been clinically observed.[5] Such a rigid envelope can initiate and maintain hypertension.[4,15]

The Page phenomenon of perirenal constriction is not the sole etiologic factor that need be invoked in the discussion of this patient's hypertension. Renal ischemia secondary to compromise of renal artery blood flow, simulating the effects of the Goldblatt clamp,[6] has been clinically observed in tumors[1,8] and conceivably was operative here.

Although radiation nephritis has been described in children as one of the sequelae of radiation therapy,[7,11] there was no histologic evidence for it in this case. Prior to necropsy, however, it could not be excluded as a contributing cause of hypertension. Finally, hypertension has been seen in patients with Wilms' tumor in whom none of the above causes were manifest.[2,3]

SUMMARY AND CONCLUSIONS

Arteriograms in a 2½ year old child precisely demonstrated a massive, subcapsular, perirenal hematoma and Wilms' tumor and, thereby, altered the initial clinical impression. The relationship of the angiographic findings to the patient's hypertension is discussed. The potential usefulness of arteriography in the differential diagnosis of abdominal masses in a pediatric population is evident.

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THE OSMOTIC EFFECTS OF METHYLGLUCAMINE DIATRIZOATE (RENOGRAFIN 60) IN INTRAVENOUS UROGRAPHY IN INFANTS

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ROENTGENOGRAPHIC contrast media of the diatrizoate type, though less toxic than their predecessors,[12] can produce profound physiologic changes when administered intravenously or orally, particularly in infants. Two recent investigations of the osmotic effects of these media were prompted by the clinical observation of hypovolemia following oral administration of gastrografin*[10] and by the reported death of a 4 month old infant following repeated injections of renovist.*[9] The reports concluded that both media had hyperosmolaric effects and that unless used judiciously, could produce disastrous reactions, particularly in small patients.

At The Montreal Children's Hospital, relatively large doses of renografin 60† are used routinely for intravenous urography in infants. Although no major untoward reactions attributable to the contrast medium have occurred in our department, the above mentioned reports stimulated us to study the osmotic effects produced by our own method of examination.

PATIENT MATERIAL AND METHODS

A preliminary study was carried out in 9 infants who had been referred to the Department of Radiology for urographic examination because of extrophy of the bladder, multiple congenital anomalies, failure to thrive, and urinary tract infection. The patients ranged in age from 6 weeks to 9 months, and in weight from 4.1 to 7.4 kg. The preparation followed the usual procedure, *i.e.*, dulcolax‡ enemas prior to the examination, and no restriction of food or fluid intake at any time before, during or following urography. None of the infants was febrile or azotemic at the time of the investigation.

Blood samples for determination of serum osmolarity, hematocrit, sodium concentration, and blood urea nitrogen were taken from a scalp or antecubital vein with a 21 gauge needle prior to, and 3 minutes, 15 minutes, 1 hour, and 4 hours following the injection of contrast medium. The preinjection sample was used to provide control data for each patient. Renografin 60 was injected via a 23 gauge needle, into a vein remote from that used for sampling. Our regular dose was used—5 ml. (3,000 mg.) of renografin 60 per kilogram of body weight for infants weighing less than 5 kg., with a maximum dose of 25 ml. (15,000 mg.) for those weighing 5 kg. or more. One child, weighing 4.1 kg., received the full 25 ml. dose in error, corresponding to 6.1 ml. (3,660 mg.) per kg. with no appreciable difference in the biochemical results. The average dose was 4.7 ml. (2,820 mg.) per kg., with a range of 3.4 to 6.1 ml. (2,040 to 3,660 mg.) per kg. The injection time was kept as short as the viscosity of the contrast medium, the bore of the needle, and the size of the vein would allow; it varied between 1 and 2½ minutes, the average being 90 seconds. Roentgenograms were made prior to injection, and immediately following each postinjection blood sample. Micturition cystourethrograms were also obtained in several patients by the excretory

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* Sodium and methylglucamine diatrizoate (E. R. Squibb & Sons Ltd.).

† Methylglucamine diatrizoate (E. R. Squibb & Sons Ltd.).

‡ Bisacodyl (Boehringer Ingelheim).

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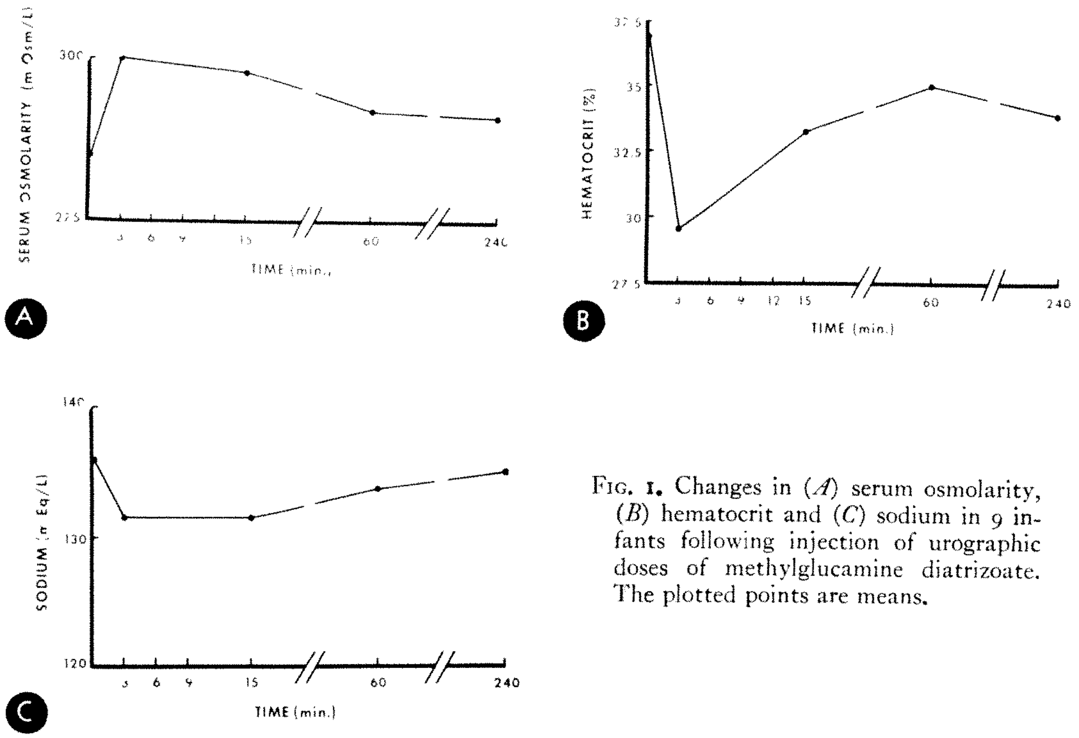

FIG. 1. Changes in (*A*) serum osmolarity, (*B*) hematocrit and (*C*) sodium in 9 infants following injection of urographic doses of methylglucamine diatrizoate. The plotted points are means.

method,[7] and none of the infants had catheterization of the bladder performed either to obtain a sample of urine or to introduce contrast medium.

Osmolarity was determined cryoscopically, with a Fiske Osmometer (accuracy ±2 mOsm/L). Sodium analyses were made in a Coleman Flame Photometer (accuracy ±2 mEq/L). Blood urea nitrogen was determined in a Technicon Auto-Analyser. The blood samples for hematocrit determination were collected directly from the plastic tubing of the sampling needle into heparinized capillary tubes, and the hematocrit was determined using an International Micro-Capillary Centrifuge and Reader.

The osmolarity of methylglucamine diatrizoate was determined, and was found to be 1,400 mOsm/L; its sodium concentration was 168 mEq/L (hypaque sodium 50 was found to have an osmolarity of 1,170 mOsm/L and a sodium concentration of 769 mEq/L).

When the results of this preliminary investigation were analyzed statistically,* significant changes in osmolarity, hematocrit, and sodium concentration were found (Fig. 1, *A*, *B* and *C*). Younger infants tended to show greater changes than older ones. A second, more detailed study was therefore performed to determine the pattern of changes in younger infants, using the same dosage schedule of renografin 60. In order to evaluate the timing and extent of changes in osmolarity and hematocrit, the technique was modified as follows: 2 samples were obtained in each infant just prior to injection, and 6 to 8 samples at 30 seconds to 1 minute intervals during the first 6 minutes following the start of the injection. In this study only osmolarity and hematocrit values were determined. The samples were obtained from an external jugular vein, using a 21 gauge needle with attached polyethylene tubing, the tubing having a capacity of 5 drops of blood. This amount was discarded immediately before each sampling. The injection site was either an antecubital or a hand vein. The procedure was otherwise the same as for the preliminary study.

Four infants were studied: Two were 4½

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* Statistical analysis (paired comparison technique) by D. F. Bray, Ph.D., Department of Genetics, McGill University.

Table I

CHANGES IN SERUM OSMOLARITY, SODIUM CONCENTRATION, BLOOD UREA NITROGEN, AND HEMATOCRIT FOLLOWING INJECTION OF METHYLGLUCAMINE DIATRIZOATE IN 9 INFANTS (6 WK. TO 9 MO.)

Time (minutes post injection)	Osmolarity (mOsm/L)	Hematocrit (per cent)	Sodium (mEq/L)	Blood Urea Nitrogen (mg./100 ml.)
	Mean ± S.D.	Mean ± S.D.	Mean ± S.D.	Mean ± S.D.
3	+15.0 ±3.7	−7.4 ±0.8	−4.6 ±1.1	−0.4 ±0.3
15	+12.8 ±5.0*	−3.6 ±0.8*	−4.3 ±1.4	−0.3 ±0.5
60	+ 6.6 ±5.1*	−1.8 ±0.6	−2.2 ±2.9*	−0.1 ±0.8*
240	+ 6.6 ±5.2*	−2.8 ±0.7	−0.5 ±3.0*	−1.2 ±1.2*

* Only 8 samples available for analysis.

months of age, weighing 4.8 and 5.5 kg. respectively. One was 3 weeks old and weighed 2.8 kg. The other, though 6 weeks of age, weighed only 2.9 kg., having been born at 29 weeks of gestation.

RESULTS

The results of *the preliminary study* are summarized in Table 1 and Figure 1, *A*, *B* and *C*. The range of pre-injection serum osmolarities for the 9 patients was 266 to 296 mOsm/L, with a mean of 285 mOsm/L. In all patients an increase in osmolarity occurred 3 minutes after injection of renografin 60. The increases ranged from 6 to 39 mOsm/L with a mean of 15 mOsm/L or 5.3 per cent of the pre-injection value (15 mOsm/L significantly different from zero; $p=.01$). The 15 minute, 1 hour, and 4 hour samples showed a return towards pre-injection values. At 4 hours the mean value was still 6.6 mOsm/L higher than prior to injection, though statistically the difference was not significantly different from zero.

Pre-injection hematocrit values varied between 32 and 43 per cent, the mean being 37. Three minutes after the injection, the hematocrit had decreased by 4 to 11%, the mean change being −7.4% ±.835. The hematocrit also tended to return toward normal in the later samples, but the differences remained significantly different from zero ($p=.05$ or .01).

At 3 minutes, serum sodium concentration was consistently decreased by 2 to 12 mEq/L (mean decrease −4.6 ± 1.05 mEq/L, $p=.01$), and at 15 minutes was still appreciably lower ($p=.05$) than prior to injection. No significant deviation from normal was evident at 1 or 4 hours.

Blood urea nitrogen concentrations showed no significant change from baseline levels.

The relationship between each of the significantly altered parameters was examined at the time of greatest deviation, *i.e.*, in the 3 minute sample. No relationship was found between serum osmolarity and sodium concentration, nor between sodium and hematocrit, but there was a strong suggestion of a relationship between serum osmolarity and hematocrit ($p=.10$) in that 40 per cent of the variation in one is accountable by the other.

In *the second study* (Fig. 2) rapid changes in osmolarity and hematocrit were evident immediately after the start of the injection. There followed a gradual return toward normal. The maximum changes occurred from 1 to 2½ minutes following the start of injection (*i.e.*, approximately at the end of the injection).

Thus, in the preliminary study, the samples taken 3 minutes following completion of the injection were probably taken when the return toward normal was already under way.

DISCUSSION

In the Department of Radiology of The Montreal Children's Hospital, approxi-

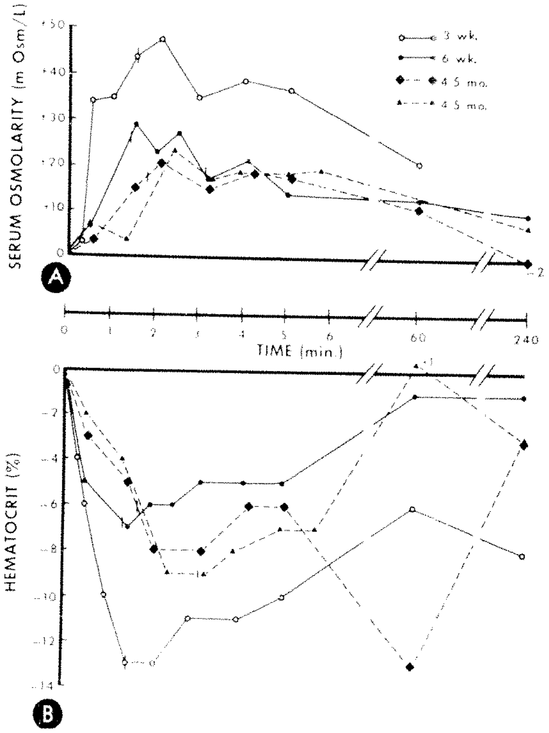

Fig. 2. Changes in (*A*) serum osmolarity and (*B*) hematocrit in 4 infants, during and after the injection of urographic doses of methylglucamine diatrizoate (renografin 60). The plotted points represent the increase in serum osmolarity and decrease of hematocrit values. The duration of the injection is represented by vertical bars on each curve.

mately 80 per cent of infants under 1 year of age who are referred for urography have micturition cystourethrographies performed as an integral part of the examination. The contrast-containing urine in the bladder is of adequate density to provide roentgenograms of diagnostic quality. A technique has been developed for obtaining single roentgenograms or cine-studies of micturition when the baby voids spontaneously.[7]

Although large doses of contrast medium do not increase the iodine concentration of the excreted urine,[13] we employ doses of renografin 60 up to 5 times those usually recommended* for infants in order to get adequate and sufficiently prolonged filling of the entire urinary tract, as well as repeated filling of the urinary bladder for cystourethrography without reinjection. We have observed no serious reactions since instituting a dosage regimen of 5 ml. (3,000 mg.) of renografin 60 per kg. up to a maximum of 25 ml. (15,000 mg.).

The two present studies show that these doses of contrast medium exerted a significant osmotic effect, particularly in younger infants. The changes occurred almost immediately following the start of injection. The drop in hematocrit was coincidental with the rise in osmolarity, indicating that fluid was being drawn rapidly into the vascular compartment. The changes were less striking but still significant 15 minutes after the injection. Therefore a cumulative effect could be expected if a repeat injection had been made within this 15 minute period. At 1 and 4 hours the serum osmolarity changes were no longer significant, indicating that serum osmolarity and intravascular fluid volume had returned toward pre-injection values. Continued significant depression of the hematocrit values, however, suggests that return to normal is quite prolonged.

Several authors have reported on the neurologic effects of contrast media and other hypertonic solutions. Sotos *et al.*[20] showed that infusions of hypertonic solutions into rabbits, sufficient to raise plasma osmolarity above 330 mOsm/L, could cause serious neurologic disturbance due to cerebral dehydration. Levels of approximately 450 mOsm/L could cause death. In a further study,[21] they oberved that prolonged hypertonicity of body fluids could disturb cellular metabolism, resulting in severe metabolic acidosis. This acidosis was diminished when normal osmolarity was restored by rehydration. Luttrell *et al.*[15] found that experimental hypertonicity in cats, if present for 5 minutes, could produce cerebral dehydration, a fall in cerebrospinal fluid pressure, and subdural and intracerebral hemorrhage. Hypertonic solutions can also produce endothelial damage, particularly in cerebral vessels, so that the blood-brain barrier is disrupted.[3,4] Even the newer contrast media produce more damage than glucose and electrolyte solutions of the same osmolarity. Thus such solutions, in addition to their hypertonicity, may be chemotoxic to vascular endothelium.[12,17,23]

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* Renografin 60, OJ-025/J2-016-364 (E. R. Squibb & Sons Ltd.).

The cardiovascular and respiratory effects of hypertonic solutions, including contrast media, have also been studied, with particular reference to angiocardiography. In 1954, Cotrim[5] observed the cardiac and respiratory effects of intravenous diodone and iodoxyl* in dogs. The amount and concentration of the dose injected, as well as the rate of administration, were all found to be of great importance. By injecting sodium chloride solutions of the same osmolarity as the contrast media, under identical conditions, he showed that the tonicity of the solutions was the principal cause of the effects observed. Cotrim suggested that the molecular concentration of the injected solutions was more important than their chemical composition in causing the cardiac and respiratory disturbances. Read[19] found that hemagglutination followed intravenous injection of concentrated radiopaque agents. This caused obstruction to pulmonary blood flow, pulmonary hypertension and acute cor pulmonale. Late peripheral vasodilatation was regularly observed, following the injection.

In 1961, Bernstein *et al.*[2] injected large doses of 90 per cent hypaque sodium into the inferior vena cava of dogs in less than 5 seconds. They found the LD_{50} to be 3 ml. (2,700 mg.) per kg. and the LD_{100} to be 5 ml. (4,500 mg.) per kg. Death usually occurred within 1 minute, preceded by acute hypotension and marked electrocardiographic abnormalities. The authors postulated that some of the cardiac effects were due to direct chemotoxic action by the contrast medium on the intrinsic cardiac regulatory and conduction mechanisms.

In our department, a 4 kg. infant receives a total of 12,000 mg. of renografin 60 for intravenous urography. In an infant of this weight, the plasma volume is about 200 ml. and the serum osmolarity approximately 280 mOsm/L. Intravenous injection of 20 ml. (12,000 mg.) of the contrast medium (the osmolarity of which is 5 times that of normal serum) could raise serum osmolarity to 380 mOsm/L (an increase of more than 30 per cent), assuming instantaneous injection and mixing. Such a change could be disastrous. Fortunately, it is virtually impossible to inject this viscous material through a No. 23 needle into the superficial veins of small infants at a rapid rate (it takes a minimum of 40 seconds to push through 20 ml. of renografin 60 using a No. 23 scalp vein needle). It follows that if less viscous contrast media became more widely accepted for intravenous urography, strict control of the rate of injection should be maintained.

Any attempt at dehydration by restriction of fluid intake prior to the examination might enhance the osmotic effects of the contrast medium. Indeed, in experimental animals, prior induction of hypervolemia with blood or dextran has been shown to protect against the injurious effects of hyperosmolarity.[8,20,21]

Several authors have recommended a second injection in intravenous urography, where necessary.[22] We have occasionally used this procedure, and found it valuable. However, the present investigation suggests that a second injection in infants should not be given until at least 15 minutes after the initial one, when large doses are being used.

The reactions which occasionally occur following small doses of contrast media have not been explained satisfactorily. We are aware of no documented instances of such reactions in infants.

SUMMARY

The effects of relatively large doses of renografin 60 on serum osmolarity, sodium concentration, blood urea nitrogen and hematocrit have been studied in 13 young infants during intravenous urography. Serum osmolarity showed a significant rise,

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* Pyridine derivatives.

reaching a peak about 90 seconds after the start of injection. There was a corresponding significant fall in hematocrit. Thereafter, both values tended to return towards normal over a period of 4 hours.

When large doses of contrast agents are used for intravenous urography in infants, a relatively slow rate of injection is the principal safety factor minimizing the risk of serious reaction to the sudden increase in plasma osmolarity. The foregoing data, coupled with previous studies, suggest that restriction of fluid intake prior to intravenous urography in infants is contraindicated.

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* * *

A SIMPLE ABDOMINAL COMPRESSOR FOR USE IN INTRAVENOUS UROGRAPHY*

By OLE EKLÖF, M.D.
STOCKHOLM, SWEDEN

INCREASED knowledge of the pathophysiology of the kidneys and newer therapeutic techniques have made increased demands on urologic roentgenologic diagnosis. Great technical progress, especially in the development of improved contrast media, has led to the acceptance of urography as a standard method both for determination of anatomic conditions and for the study of kidney function.[3]

Soon after the introduction of urography as a method of examination, it was found that adequate filling of the renal pelvis and ureters, a necessary condition from a diagnostic point of view, could frequently be achieved only by producing a temporary occlusion of the ureters in some mechanical manner. In spite of the remarkable progress in the technique of urography, there is still an apparent need for an effective ureteric compression device, both in children and adults.

METHOD AND PROCEDURE

In Sweden, Steinert's[4] apparatus is probably the one most generally employed. It consists of 2 inflatable rubber balloons, one of which is placed over each ureter, fastened over the lower part of the patient's abdomen by a plastic sheet and leather or cloth straps. In order to facilitate a more accurate regulation of the pressure, the apparatus is furnished with a valve device and a manometer.

However, this apparatus has certain disadvantages. The initial expense is substantial and the rubber balloons and tubing have to be replaced eventually. The taps and manometer require constant supervision. But most important, particularly when examining children, is the tendency of the rubber balloons to change shape and position during compression. Even the use of small cloth bags around the balloons does not prevent this. As a consequence, undesirable compression of the aorta and inferior vena cava is noted. This pressure may cause a fall in blood pressure with supression of urine secretion, which has been clinically observed by Wickbom,[5] among other investigators, and has been demonstrated in animal experiments by Edling *et al.*[2] Furthermore, such a fall in blood pressure, especially when examining children, is a very unpleasant symptomatic complication, although in most cases the situation can be readily controlled.

For the last year and a half, the Department of Diagnostic Roentgenology at the Children's Clinic, Karolinska Sjukhuset, has used the compressor constructed by Billing[1] with good results. It is both inexpensive and durable. It does not require any particular supervision in the way of repairs and is easy to use. When properly applied, its construction ensures that the aorta and the vena cava are not subjected to compression.

Our compressor was constructed in the carpenter's workshop at the hospital. It is available in three sizes, intended for children in different age groups (Fig. 1 and 2). The apparatus consists of 2 wooden blocks fastened by screws and winged nuts to a veneer sheet, each block being adjustable in a lateral slot in the wooden sheet (Fig. 3). The blocks should never be brought nearer to each other than about 3 cm. In this way sufficient space is allowed for the aorta and the inferior vena cava. Each block can be rotated around its axis (the screw). The compressor is fastened in the usual way over the lower part of the patient's abdomen by leather or cloth straps which pass around his body (Fig. 4). On application, the blocks are rotated so that they extend as far as possible longitudinally over the ureters. It is advantageous to place a foam-plastic sheet, about 1 cm. thick, between the blocks and the patient's abdomen. This sheet, when folded over the flanks, protects them from the pressure of the straps. One can learn very quickly to estimate the necessary compression pressure, which is considerably less than is assumed in general.

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* Presented at the Twenty-sixth Northern Congress of Roentgenology, Helsingfors, Finland, June 3-6, 1964.
From the Department of Diagnostic Roentgenology, Children's Clinic, Karolinska Sjukhuset, Stockholm, Sweden.

Up to the present, the compressor has been used for about 500 urographic examinations in children of all ages over 2 months and is the only type of compressor which is now employed in our clinic. We have not found it to have any disadvantages. On no occasion has it been necessary to discontinue an investigation on account of a fall in blood pressure.

When properly applied, it produces a perfectly satisfactory compression, and, at the same time, it is obvious that the patient's subjective discomfort in connection with the investigation is less than that

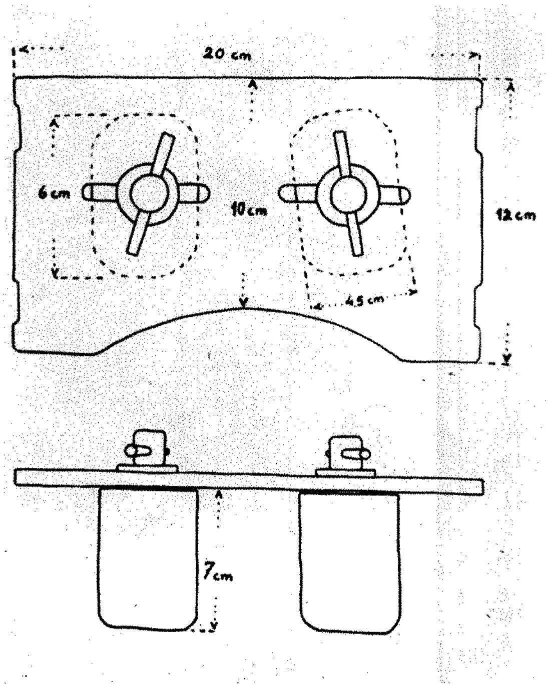

Fig. 1. A sketch of the compressor, medium size.

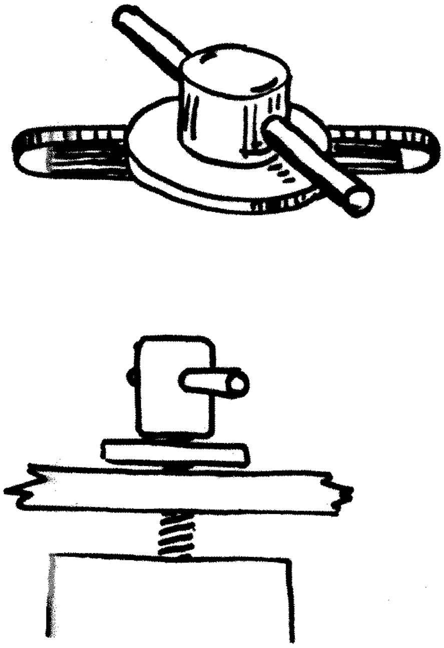

Fig. 2. A detail drawing of the compressor.

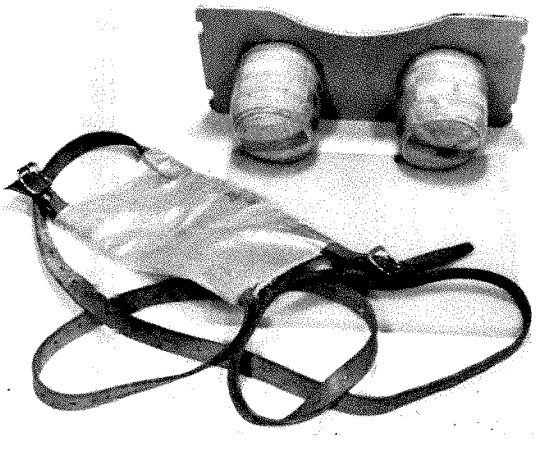

Fig. 3. The compressor with components ready for application.

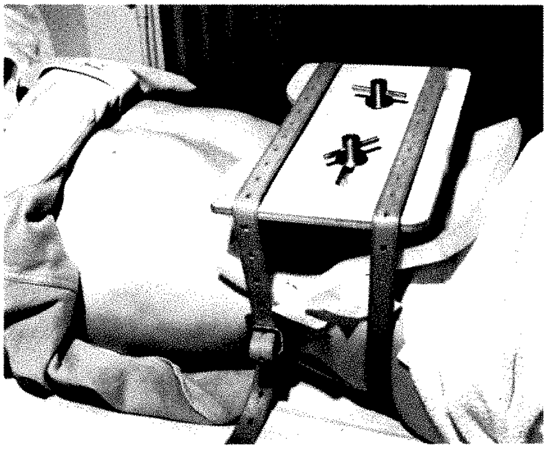

Fig. 4. The compressor in use.

caused by the previously employed type of compressor, where inflated rubber balloons were utilized.

The compressor has been used at Karolinska Sjukhuset, also for examination of adult patients, with the same good results.

SUMMARY

A simple abdominal compressor for use in intravenous urography is described. It has proved extremely suitable for urographic examination in children and has been used also with good results in adults.

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Forty-seventh Annual Meeting: Roosevelt Hotel, New Orleans, La., April 8–10, 1965.

EDITORIALS

THE PROBLEM OF COMPRESSION IN INTRAVENOUS PYELOGRAPHY

IT IS good practice for radiologists to re-evaluate periodically technical procedures which may or may not be used. Such a procedure is external compression of the ureters during the course of intravenous pyelography. It is not proposed to discuss the indications and contraindications of compression, but simply its effectiveness when it *is* used.

The radiologic literature abounds in favorable *qualitative* appraisal of compression; aware of the caprice of subjective impression, we scouted the more recent literature for *quantitative* appraisal.

Bernstein and Hamby,[1] in an effort to obtain unilateral sampling of urine, were able to occlude each ureter by an externally applied wooden block of their own design. The effectiveness of their compression was demonstrated qualitatively by the absence of contrast-laden urine in the bladder, and quantitatively by renal clearance (creatinine and urea) studies; the sum of clearance of each kidney (with the opposite kidney's ureter occluded) approximated the clearance with neither ureter occluded. Their compression block was applied at the point where the ureter crosses the common iliac artery at the pelvic inlet; decreased femoral pulsation attested to both the correct position of the block and its effectiveness.

Dihlmann[2] compared quantitatively 200 intravenous pyelograms with compression and 200 without. Using a relatively crude compression with a football bladder, he found that the probability of obtaining good filling of the renal collecting system was roughly doubled. Without compression, the collecting system was completely filled in 25 per cent and with compression in 69 per cent; without compression, the right ureter was completely visualized (by combining the filled segments on the several exposures) in 32 per cent and the left ureter in 25 per cent, whereas with compression, the right ureter was visualized in 55 per cent and the left ureter in 53 per cent.

The most ingenuous of the quantitative studies and the freest of taint from subjective error was that of Ludin.[3] As a criterion of the effect of compression, he measured the increase in the frontal area of the collecting system in 205 patients before and after compression with a device consisting of a single balloon and a double balloon, and subjected the data obtained to rigorous statistical treatment. The frontal area of the collecting system increased by 80 per cent following compression with a double balloon and only by 40 per cent after compression with a single balloon, as compared to the area when no compression was used.

These data suggest that the effectiveness of compression cannot be considered apart from the design of the device used for compression. The earliest device was a crude bolus of cloth beneath a band fixed to the table, "pressed into the abdominal cavity until the patient complained." This gave way to an air-filled balloon, further refined by measuring the air pressure used. Then, based on greater regard for local anatomy, two indenting devices were employed, which were designed to nestle one on either side of the sacral promontory and compress each ureter separately as it coursed over the pelvic brim. Such devices consisted of tennis balls, halves of rubber balls, variously fashioned balsa blocks, and small air-filled balloons.

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The next major step was to free the patient from the table by wrapping the band around him rather than fixing it to the tabletop, thereby making him more comfortable during the examination and permitting oblique studies with compression. Among devices incorporating this principle, one may mention the compression apparatus of Steinert.[4] This device contains 2 small balloons, with valves enabling independent inflation of each, connected to a manometer to measure the pressure in each balloon separately, thus allowing individualization of the examination with quantitative control.

Compression of the ureters is of definite value also in intravenous pyelography of children. In this issue of the Journal, Eklöf[5] describes a device which he uses routinely with good results and analyzes the advantages which may be derived from such a procedure.

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Fredericksburg, Virginia

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ERICH M. UHLMANN, M.D.

1901–1964

> As a well-spent day brings happy sleep
> so a life well used brings happy death.
> Leonardo da Vinci

DR. ERICH MYRON UHLMANN died on September 14, 1964 at the age of 63 years after a lingering illness. For the last 25 years, Dr. Uhlmann was Director of the Tumor Clinic and of the Department of Therapeutic Radiology at Michael Reese Hospital and Medical Center in Chicago, Illinois.

Born in Bad Driburg, Germany, on April 21, 1901, Dr. Uhlmann attended the Universities of Bonn, Leipzig and Kiel. In 1923 he received the M.D. degree at The University of Heidelberg. His career as a therapeutic radiologist started in 1924 when he studied at the Radiologic Institute of The University of Frankfurt. In 1928 he became Chief of Radiotherapy of The Frankfurt University Dermatology Clinics. In 1930 he became Chief of Radiation Therapy at The University of Freiburg, a post he held until the Nazi accession to power in January, 1933. Following the war he was accorded the rank of full Professor at The University of Freiburg, a rank he held until his death.

After leaving Germany in 1933, Dr. Uhlmann went to the Tuberculosis Center in Davos, Switzerland where he conducted high altitude physiologic studies. This was followed by 6 months of research in Copenhagen. Then, in 1934, he was appointed to the faculty of The University of Istanbul in Turkey. In 1937, following a visit to Chicago as the Turkish representative to the International Congress of Radiology, Dr. Uhlmann came to Michael Reese Hospital.

Shortly thereafter, Dr. Uhlmann reported on the use of radon ointment in healing skin damaged by radiation. This technique is still employed successfully.

Dating back early in his career was Dr. Uhlmann's interest in the use of the electron beam for the treatment of cancer. World War II interrupted his efforts to build a betatron for this purpose. After the war his interest turned to the potential of the linear acceleration for high-energy electron generation. As a result of his indefatigable efforts, official government secrecy, Korean conflict delays and financial difficulties were overcome and he and his co-workers designed and had built a 40 mev. linear accelerator which was completed in 1954 and has been applied clinically since 1957. In addition to its clinical usage, the linear accelerator has been used experimentally to induce artificial radioactivity.

Dr. Uhlmann was Assistant Professor of Radiology at Northwestern University Medical School and Professor of Radiology at The University of Freiburg (Germany). He was a member of many national and international professional societies including The American Cancer Society; he was a member of The Board of Directors of its Illinois Division. He was a Fellow of The American College of Radiology and of The Chicago Roentgen Society of which he was a Past-President and at the time of his death a member of The Board of Directors. Dr. Uhlmann also held membership in The Inter-American College of Radiology, The American Roentgen Ray Society, The Radiological Society of North America, The American Medical Association, and others. He was a co-editor of The Encyclopedia of Medical Radiology and of *Der Radiologe*. He was a Senior Attending Physician on the medical staff of Michael Reese Hospital and Medical Center and a consultant in Radiotherapy, Hines Veterans Administration Hospital.

In addition to his professional accomplishments, Dr. Uhlmann was a man of many talents and varied interests. He was fond of outdoor sports and was an expert skier, mountain climber and equestrian. A cultured gentleman, he and his charming wife, Ilsa, who passed away in April, 1963 had a wide circle of close friends. An evening with the Uhlmanns meant enjoyment of true Gemütlichkeit among musicians, painters, sculptors, and other persons of talent. Erich himself was a fine musician and a lover of fine music. And he was more than able to hold his own in discussions of the Talmud and its commentaries.

Though he found pleasure in his professional attainments and cultural activities, Dr. Uhlmann's greatest delight was the growth and maturation of his three sons, Gary, Frank and Peter. He was truly proud of their scholastic achievements, their social interests, and their devotion to each other. The parents had set fine examples; the sons followed in their path.

Dr. Uhlmann died of cancer, the hunter unmercifully turned upon by his prey.

His associates at Michael Reese Hospital and in radiology and numerous others will long remember and long miss their physician, friend, teacher, and counsellor.

Bertram Levin, M.D.
Michael Reese Hospital
Chicago, Illinois 60616

MUSEUM OF THE AMERICAN COLLEGE OF RADIOLOGY

The American College of Radiology Foundation

THE inscription on the façade of the Archives Building in Washington, D. C., reads: "WHAT IS PAST IS PRESENT."

Although the primary responsibility of the American College of Radiology is the promotion of radiologic practice through a joint consideration of scientific and socioeconomic aspects, conditions now make it mandatory that it be increasingly responsive to new needs by establishing new dimensions and by a greater emphasis on cultural and heritable aspects such as the Museum, the History, the Library, etc.—aspects which I like to refer to collectively as the "fine arts of radiology" or the "radiologic humanities."

The Executive Committee of the American College of Radiology Foundation during its meeting in San Francisco in June, 1964 approved the following: (1) The appointment of Mr. Robert T. Morrison of the Eastman House as Curator of the Museum, which is now a combined function of the Foundation and the Council for Radiologic Heritage, of which Dr. Edwin Ernst is Chairman, and (2) the empowering of the Museum Committee and Mr. Morrison to initiate and carry out an intensive search for and location, identification, authentication and registration of all possible pieces of equipment and memorabilia.

Our immediate interest is the Museum Committee, which is dedicated to the ideal of rendering educational and cultural services to the radiologic community through the use of items of heritage. The Museum will further its aims by presenting through the use of its collection an intimate and authentic survey of the origins, the development and the present status of radiology, thus reflecting the story of our achievements in terms of time and importance. The Museum will reflect and punctuate the pulse beat of radiologic time and will ensure that the continuous past will flow smoothly into the unpredictable future. It will be a depository for items which must be preserved because of their esthetic historic or scientific importance. It will be dedicated to the creation of an atmosphere of contemplation in its exhibit halls where the visitor may gain intellectual radiologic stimulation while enjoying the actual exhibits. It will serve as a permanent memorial to our radiologic forebears.

M. H. Poppel, M.D.
Chairman, Museum Committee
American College of Radiology Foundation

NEWS ITEMS

NEW OFFICERS OF THE RADIOLOGICAL SOCIETY OF NORTH AMERICA

At the Fiftieth Annual Meeting of the Radiological Society of North America held November 29 to December 4, 1964 at the Palmer House, Chicago, Illinois, the following officers were elected: *President*—Robert D. Moreton, M.D., Fort Worth, Texas; *President-Elect*—John W. Walker, M.D., Kansas City, Missouri; *First Vice-President*—Harold G. Jacobson, M.D., New York, New York; *Second Vice-President*—R. Brian Holmes, M.D., Toronto, Ontario, Canada; *Third Vice-President*—Gerald M. Mc Donnel, M.D., Los Angeles, California; *Secretary-Treasurer*—Maurice D. Frazer, M.D., Lincoln, Nebraska; and *Historian*—Howard P. Doub, M.D., Detroit, Michigan. The new *Chairman of the Board of Directors* is Stanley M. Wyman, M.D., Boston, Massachusetts.

The Gold Medal of the Society was awarded to H. Dabney Kerr, M.D., Saint Michaels, Maryland.

The Fifty-first Annual Meeting of the Society will be held November 28–December 3, 1965 at the Palmer House in Chicago, Illinois.

NEW YORK ROENTGEN SOCIETY

The New York Roentgen Society will hold its Second Annual Spring Conference at the Waldorf-Astoria Hotel on April 29, 30, and May 1, 1965.

The Scientific Program, with Dr. William Seaman as Chairman, will feature refresher courses as well as papers on subjects of current interest. The Annual Ross Golden Lecture will be given by Dr. Earl Miller. Other nationally known radiologists will participate in the meeting, which coincides with the re-opening of the World's Fair.

For additional information, write to Albert A. Dunn, M.D., General Chairman, The Roosevelt Hospital, 428 West 59th Street, New York, New York 10019.

POSTGRADUATE COURSE IN RADIOISOTOPE SCANNING AT EMORY UNIVERSITY

The Department of Radiology, Division of Nuclear Medicine, of Emory University School of Medicine will conduct a Postgraduate Course in "Radioisotope Scanning in Clinical Practice," April 23 and 24, 1965 at the Grady Memorial Hospital, Atlanta, Georgia.

The guest faculty will include Drs. David Charkes, William Eyler, Phillip Johnson, James Quinn, Bruce Sodee, Henry Wagner, Jr., and Mr. Craig Harris.

Further information may be obtained from H. S. Weens, M.D., Department of Radiology, Emory University School of Medicine, Atlanta, Georgia 30322.

COURSE IN CLINICAL USE OF RADIOACTIVE ISOTOPES

A course in the "Clinical Use of Radioactive Isotopes" will be given under the supervision of Dr. Sergei Feitelberg, Dr. Solomon Silver and Dr. Edith Quimby of the Department of Radiology, Columbia University, New York City, from May 31 through June 25, 1965.

This is a full-time course consisting of lectures, experimental laboratory exercises, clinical rounds and clinical measurements on patients and on specimens.

In addition to Drs. Feitelberg, Silver and Quimby, the teaching staff will include a number of invited lecturers from the New York area, each presenting material in his own special field.

Enrollment in the class is limited to 20.

Inquiries should be addressed to Dr. Sergei Feitelberg, Mt. Sinai Hospital, Fifth Avenue at 100th Street, New York, New York.

DR. EUGENE P. PENDERGRASS HONORED

Dr. Eugene P. Pendergrass, Emeritus Professor of Radiology at the University of Pennsylvania School of Medicine, has been named the first Matthew J. Wilson Professor of Research Radiology.

This professorship, created in 1961, was made possible by gifts from Mr. and Mrs. Matthew J. Wilson, Jr., and Mrs. Fred C. Newcombe. Mr. Wilson, Jr., who died in 1963, was the son and Mrs. Newcombe is the daughter of the distinguished Philadelphia physician and civic leader after whom the chair is named.

The gifts by which the Wilson professorship was created are valued at more than $500,000, thus making the chair one of the most highly endowed at the University. The chair was officially established by the University on May 31, 1961, the 100th anniversary of Dr. Wilson's birth.

Dr. Pendergrass is also Director of the University of Pennsylvania School of Medicine Bicentennial Observance, celebrating the founding of the Pennsylvania School of Medicine—the Nation's first—in 1765.

SYMPOSIUM ON GENITO-URINARY DISEASE

The Department of Radiology of the University of Kentucky College of Medicine will conduct a Symposium on Genito-Urinary Disease from March 29th to April 2nd, 1965. The program is designed to appeal to physicians and surgeons interested in the genito-urinary system as well as radiologists. Besides lectures on topics of current interest, the program will feature panel discussions on Bladder Outlet Obstruction in Childhood, Renovascular Hypertension, Cystic Disease of the Kidney, Carcinoma of the Cervix, and Tumors of the Ovary.

Besides many members of the faculty of the University of Kentucky College of Medicine, the following guest speakers will participate: Lawrence A. Davis, M.D., Louisville, Kentucky; John L. Emmett, M.D., Rochester, Minnesota; John A. Evans, M.D., New York, New York; C. Paul Hodgkinson, M.D., Detroit, Michigan; John W. Hope, M.D., Philadelphia, Pennsylvania; John A. Hutch, M.D., San Francisco, California; Bertram Levin, M.D., Chicago, Illinois; Robert Lich, Jr., M.D., Louisville, Kentucky; Alphonse Palubinskas, M.D., San Francisco, California; Charles E. Shopfner, M.D., Kansas City, Missouri; Frederic N. Silverman, M.D., Cincinnati, Ohio; Kaighn Smith, M.D., Philadelphia, Pennsylvania; and Theodore A. Tristan, M.D., Philadelphia, Pennsylvania.

Further information may be obtained from Nicholas J. Pisacano, M.D., Director, Continuing Education, University of Kentucky College of Medicine, Lexington, Kentucky 40506.

THE AMERICAN SOCIETY OF RADIOLOGIC TECHNOLOGISTS

The American Society of Radiologic Technologists will be host to the Fourth International Meeting to be held June 5–10, 1965, at the Sheraton-Chicago Hotel, Chicago, Illinois.

An excellent program has been prepared, consisting of formal papers, symposia, workshops and refresher courses. A large turnout of Canadian and American technologists is expected.

For further information, please contact Ruth C. Jaffke, R.T., M.T., Publicity Chairman, 13701 South School Street, Riverdale, Illinois 60627.

BOOK REVIEW

Books sent for review are ackonwledged under: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interest of our readers as space permits.

Protection against Ionizing Radiations. A Survey of Existing Legislation. Offprint from Volume 15, No. 2 of the International Digest of Health Legislation; World Health Organization, Geneva. Published in English and French. Paper. Pp. 170. Price, $2.00. Available through Columbia University Press, International Documents Service, 2960 Broadway, New York, N. Y. 10027.

This is an offprint of the Survey of Existing Legislation on Protection against Ionizing Radiations, which was originally published in the *International Digest of Health Legislation*, 1964, *15*, 209–376, by the World Health Organization (WHO), a specialized agency of the United Nations. The survey is based on such source material as was available at the Headquarters of the WHO up to the end of May, 1964.

As stated in the preface, it is not intended to provide an exhaustive coverage of world legislation in the field in question, but to give typical examples of the form that such legislation has taken.

In the introduction, some of the tragic early experiences with the use of roentgen rays are cited, emphasizing the need for measures to ensure adequate protection. Standards and Instructions were published by some of the national radiologic bodies, including the National Committee on Radiation Protection in the U.S.A., since 1905. The major step forward, however, was taken at the Second International Congress of Radiology held in Stockholm, in 1928 with the creation of the International X-Ray and Radium Protection Commission, which in 1950 became the International Commission of Radiological Protection (ICRP). The great contributions of this first international body are reviewed and its salient recommendations are stressed. The role of other agencies, as for instance the ENEA (European Nuclear Energy Agency) formed in 1957 and the IAEA (International Atomic Energy Agency) which in 1962 likewise adopted basic "radiation protection norms," is also briefly discussed.

In the chapter of General Survey of Legislation, it is pointed out that a comparative survey made in 26 countries revealed that there are two attitudes to this question. In certain countries, the attitude has been taken that legislation should be kept to a minimum since the technical aspects of the uses of radiation and the methods employed for protection are continuously changing. The other attitude is to introduce legislation covering more or less the whole field of radiation protection in an extremely detailed manner, although even so, such legislation is usually in the form of regulations which, in principle, can be more rapidly amended than laws.

In subsequent chapters, the pertinent legislation is reviewed separately for the following countries: Australia, Austria, Belgium, Brazil, Canada, Czechoslovakia, Denmark, Finland, France, Germany (Federal Republic), Iceland, Italy, Luxembourg, Netherlands, New Zealand, Norway, Philippines, Poland, Portugal, South Africa, Spain, Sweden, Switzerland, Union of Soviet Socialist Republics, United Kingdom and the United States of America.

The over-all conclusion is reached that there is a fair degree of uniformity at the national level as to certain of the technical aspects of the question.

T. Leucutia, M.D.

BOOKS RECEIVED

Roentgenography and Roentgenology of the Middle Ear and Mastoid Process. By Lewis E. Etter, B.S., M.D., F.A.C.R., Professor of Radiology, Western Psychiatric Institute and Clinic, The Falk Clinic, School of Medicine, University of Pittsburgh; Consultant, C. Howard Marcy State Hospital, Pittsburgh, Pa. With the collaboration of Lawrence C. Cross, R.T., Chief Research X-ray Technician, Western Psychiatric Institute and Clinic; Chief X-ray Technician, Veterans Administration Hospital, Leech Farm, Pittsburgh, Pa., and Merle J. Stuart, R.T., Research X-ray Technician, Western Psychiatric Institute and Clinic, The Falk Clinic, School of Medicine, University of Pittsburgh, Pittsburgh, Pa. With a foreword by Kenneth M. Day, M.D. Cloth. Pp. 149, with 134 figures. Price, $9.75. Charles C Thomas, Publisher, 301–327 East Lawrence Avenue, Springfield, Ill., 1964.

The Physics of Radiology. Second edition (revised second printing). American Lecture Series, Publication Number 419. By Harold Elford Johns, M.A., Ph.D., F.R.S.C., LI.D., Professor and Head, Department of Medical Biophysics; Professor of Physics, University of Toronto; Head, Physics Division, Ontario Cancer Institute, Toronto, Canada. Cloth. Pp. 767, with many tables and figures. Price, $23.00. Charles C Thomas, Publisher, 301–327 East Lawrence Avenue, Springfield, Ill., 1964.

The Radiologic Clinics of North America. Symposium on Angiography in Retrospect and Prospect. December, 1964, Volume II, Number 3. Melvin M. Figley, M.D., and Philip Rubin, M.D., Guest Editors. Cloth. Pp. 221, with many illustrations. W. B. Saunders Company, Philadelphia, 1964.

Training in Radiological Protection: Curricula and Programming. Technical Reports Series No. 31. International Atomic Energy Agency, Vienna, 1964. Paper. Pp. 101. Price, $2.50. Distributed by International Publications, Inc., 317 East 34th Street, New York 16, N. Y., 1964.

Positioning in Radiography. Eighth edition. By K. C. Clark, M.B.E. Cloth. Pp. 806, with many illustrations. Price, $35.00. Intercontinental Medical Book Corporation, 381 Park Avenue, South, New York 16, N. Y., 1964.

Medical Uses of Ca^{47}. Report of the second panel on the medical uses of Ca^{47} held in Vienna, September 9–11, 1963. Technical Reports Series No. 32. Paper. Pp. 198, with some figures. Price, $4.00. International Atomic Energy Agency, Vienna, 1964. Distributed by International Publications, Inc., 317 East 34th Street, New York 16, N. Y., 1964.

Hospital Health Services. By Claire Jarett Roth, and Lillian Weiner. A "Careers for Tomorrow" book. Cloth. Pp. 117, with some illustrations. Price, $3.50. Henry Z. Walck, Inc., 19 Union Square West, New York 3, N. Y., 1964.

Mammalian Cytogenetics and Related Problems in Radiobiology. Proceedings of a symposium held at São Paulo and Rio de Janeiro, Brazil, October, 1962. Edited by C. Pavan, C. Chagas, O. Frota-Pessoa, and L. R. Caldas. Cloth. Pp. 427, with some illustrations. Price, $15.00. A Pergamon Press Book, The Macmillan Company, 60 Fifth Avenue, New York 11, N. Y., 1964.

Annual Review of Nuclear Science. Volume 14. Edited by Emilio Segrè, University of California, Berkeley, Calif.; Associate Editors, Gerhart Friedlander, Brookhaven National Laboratory, and H. Pierre Noyes, Stanford University, Palo Alto, Calif. Cloth. Pp. 510, with many tables and charts. Price, $8.50. Annual Reviews, Inc., 231 Grant Avenue, Palo Alto, Calif., 1964.

Précis de Curiethérapie: Endocuriethérapie—Plésiocuriethérapie. By B. Pierquin, Radiologiste des Hôpitaux de Paris; Chef de l'Unité de Radiothérapie Interstitielle de l'Institut Gustave-Roussy. With the collaboration of D. Chassagne, Radiologiste des Hôpitaux de Paris; Radiothérapeute de l'Institut Gustave-Roussy; and R. Pérez, Radiologiste à l'Hôpital Américain de Paris; Chef du Laboratoire des Radio-Isotopes. Preface by Robert T. Coliez. Paper. Pp. 344, with 195 figures. Masson & Cie, Éditeurs, 120, Boulevard Saint-Germain, Paris, France, 1964.

Ilio-Cavographie et Lymphographie: dans la Recherche des Adénopathies Rétropéritonéales. By H. Pujol and J. L. Lamarque. Preface by Prof. P. Lamarque. Paper. Pp. 256, with 119 figures. Price, 70 F. Masson & Cie, Éditeurs, 120, Boulevard Saint-Germain, Paris, France, 1964.

Maladies des Voies Biliaires Intrahépatiques Segmentaires. By J. Caroli, Professeur à la Faculté de Médecine de Paris; and V. Corcos Chef de Clinique à la Faculté de Médecine de Paris. Paper. Pp. 352, with 93 figures. Price, 76 F. Masson & Cie, Éditeurs, 120, Boulevard Saint-Germain, Paris, France, 1964.

Report of the United Nations Scientific Committee on the Effects of Atomic Radiation. General Assembly; Official Records; Nineteenth Session; Supplement No. 14 (A/5814). Paper. Pp. 120, with some figures. Price, $1.50. For further information write to United Nations, Sales Section, New York, N. Y. 10017, 1964.

Stimulation of the Longitudinal Growth of the Long Bones. By E. Løssl Nordentoft and E. Hjort Guldhammer. Acta Orthopaedica Scandinavica, Supplementum No. 74. Paper. Pp. 26. Munksgaard, Copenhagen, 1964.

Osteoarthritis in Lumbar Synovial Joints: A Morphologic Study. By Thord Lewin. Acta Orthopaedica Scandinavica, Supplementum 73. Paper. Pp. 112, with many illustrations. Munksgaard, Copenhagen, 1964.

Treatment for Tuberculosis of the Spine. Antituberculosis Drugs in Conjunction with Radical Operation and Short Hospitalization with No Enforced Recumbency or Immobilization. By Bernhard Paus, Department of Orthopaedic Survery, The National Medical Center, Seoul, South Korea. Acta Orthopaedica Scandinavica, Supplementum No. 72. Paper. Pp. 139, with some illustrations. Munksgaard, Copenhagen, 1964.

Postoperative Management in Lumbar Disc Protrusions. I. Indications, Method and Results. II. Follow-up on a Trained and an Untrained Group of Patients. By Jørgen W. Hansen, Department of Physical Medicine, Rigshospitalet, Copenhagen, Denmark. Acta Orthopaedica Scandinavica, Supplementum 71. Paper. Pp. 47, with some illustrations. Munksgaard, Copenhagen, 1964.

The Life and Times of Emil H. Grubbe. By Paul C. Hodges, M.D. Cloth. Pp. 135. Price, $3.95. University of Chicago Press, 5750 Ellis Avenue, Chicago 37, Ill., 1964.

Atlas of Tumor Pathology. Section IV, Fascicles 12 and 13. Tumors of the Upper Respiratory Tract and Ear. By James E. Ash, Colonel, Medical Corps, United States Army, Retired; Former Director, Armed Forces Institute of Pathology; Former Scientific Director, American Registry of Pathology; Consultant, Registries of Otolaryngologic Pathology and of Bladder Tumors, Armed Forces Institute of Pathology, Washington, D. C.; Marcus R. Beck, Colonel, Medical Corps, United States Army; Chief, Laboratory Service, Letterman General Hospital, San Francisco, Calif.; Former Chief, Ear, Nose, and Throat Section, Armed Forces Institute of Pathology, Washington, D. C.; and J. Daniel Wilkes, M.D., Associate Pathologist, Suburban Hospital, Bethesda, Md. Paper. Pp. 262, with 365 figures. Price, $2.40. American Registry of Pathology, Armed Forces Institute of Pathology, Washington, D. C., 20305.

SOCIETY PROCEEDINGS

MEETINGS OF RADIOLOGICAL SOCIETIES*

United States of America

American Roentgen Ray Society
Secretary, Dr. C. Allen Good, Mayo Clinic, Rochester, Minn. Annual meeting: Hilton Hotel, Washington, D. C., Sept. 28–Oct. 1, 1965.

American Radium Society
Secretary, Dr. John L. Pool, 444 East 68th Street, New York, N. Y. 10021. Annual meeting: Roosevelt Hotel, New Orleans, La., April 8–10, 1965.

Radiological Society of North America
Secretary-Treasurer, Dr. Maurice Doyle Frazer, 1744 South Fifty-eighth St., Lincoln, Neb. Annual meeting: Palmer House, Chicago, Ill., Nov. 28–Dec. 3, 1965.

American College of Radiology
Executive Director, William C. Stronach, 20 N. Wacker Drive, Chicago 6, Ill. Annual meeting: Bellvue Stratford Hotel, Philadelphia, Pa., Feb. 10–13, 1965.

Section on Radiology, American Medical Association
Secretary, Dr. Clyde A. Stevenson, Sacred Heart Hospital, West 101 Eight Ave., Spokane 4, Wash. Annual meeting: New York, N. Y., June 20–24, 1965.

American Board of Radiology
Secretary, Dr. H. Dabney Kerr. Correspondence should be directed to Kahler Hotel Building, Rochester, Minn.

The Spring 1965 examination will be held at the San Francisco Hilton Hotel, San Francisco, Calif., June 13–18, inclusive. This will be the last time that the Special Examination in Nuclear Medicine will be offered to physicians who are already certified in Radiology or Therapeutic Radiology. The deadline for filing applications for this examination was December 31, 1964.

The Fall 1965 examination will be held at the Statler Hilton Hotel, Dallas, Texas, December 5–10, inclusive. The deadline for filing applications for this examination is June 30, 1965.

American Association of Physicists in Medicine
Secretary-Treasurer, Charles S. Simons, University of Michigan Hospital, Ann Arbor, Mich. Annual meeting to be announced.

American Club of Therapeutic Radiologists
Secretary, Dr. J. A. del Regato, Penrose Cancer Hospital, Colorado Springs, Colo.

Eleventh International Congress of Radiology
Secretary-General, Professor Dr. Med. Arduino Ratti, via Moscova, 44-1, Milan, Italy. Address inquiries to Professor Dr. Med. Luigi Turano, President-Elect, Istituto di Radiologia, Università di Roma, Rome, Italy. Meeting: September 22–28, 1965.

Ninth Inter-American Congress of Radiology
Counselor for the United States, Dr. Philip J. Hodes, Jefferson Medical College Hospital, 11th and Walnut Streets, Philadelphia 7, Pennsylvania. Meeting: Montevideo, Uruguay, 1967.

Alabama Radiological Society
Secretary, Dr. Walter Brower, Birmingham, Ala. Meets time and place of Alabama State Medical Association.

American Nuclear Society
Treasurer, Raymond Maxson, 86 E. Randolph St., Chicago, Ill. Annual meeting to be announced.

Arizona Radiological Society
Secretary-Treasurer, Dr. George Gentner, 3435 W. Durango, Phoenix, Ariz. Two regular meetings a year. Annual meeting at time and place of State Medical Association and interim meeting six months later.

Arkansas Radiological Society
Secretary Dr. Charles W. Anderson, 1108½ Poplar, Pine Bluff, Ark. Meets every three months and also at time and place of State Medical Association.

Association of University Radiologists
Secretary-Treasurer, Dr. Alexander R. Margulis, Department of Radiology, University of California, San Francisco, Calif. Annual meeting: Seattle, Washington, May 14 and 15, 1965.

Atlanta Radiological Society
Secretary, Dr. Donald R. Rooney, Burnt Hickory Road, Marietta, Ga. Meets monthly except during three summer months, on third Tuesday, at the Academy of Medicine, Atlanta, Ga., at 8:00 P.M.

Bavarian-American Radiologic Society
Secretary, Dr. Roy R. Deffebach, Major, MC, Radiology Service, 5th General Hospital, APO 154, New York, N. Y. Meets quarterly.

Blockley Radiological Society
Secretary, Dr. Bernard J. Ostrum, 2412 North 52nd St., Philadelphia, Pa.

Bluegrass Radiological Society
Secretary-Treasurer, Dr. Daniel J. Hanson, University of Kentucky, Medical Center, Lexington, Kentucky. Meets quarterly.

Brooklyn Radiological Society
Secretary, Dr. Jay P. Sackler, Brooklyn, N. Y. Meets first Thursday of each month, October through June.

Buffalo Radiological Society
Secretary, Dr. Berkeley Zinn, 85 Wehrle Dr., Buffalo 25, N. Y. Meets second Monday evening each month, October to May inclusive.

California Radiological Society
Secretary, Dr. L. Henry Garland, Suite 1739, 450 Sutter St., San Francisco, Calif. Meets annually during meeting of California Medical Association.

Catawba Valley Radiological Society
Secretary, Dr. Emmett R. White, P. O. Box 303, Rutherford College, N. C. Meets every Tuesday, Dept. of Radiology, Valdese General Hosp., Valdese, N. C. at 12:00 P.M.

Central New York Radiological Society
Secretary-Treasurer, Dr. Edward W. Carsky, Crouse-Irving Hospital, 820 S. Crouse Ave., Syracuse, N. Y. Meets first Monday each month, October through May.

Central Ohio Radiological Society
Secretary-Treasurer, Dr. Harold W. Long, 81 S. Fifth St., Columbus 15, Ohio. Meets third Thursday in October, and second Thursday in November, January, March and May at Fort Hayes Hotel, Columbus, Ohio.

Central Society of Nuclear Medicine
Secretary, Dr. Robert S. Landauer, Radiation Center Bldg., 1903 West Harrison St., Chicago 12, Ill.

Chicago Roentgen Society
Secretary-Treasurer, Dr. Robert D. Moseley, Jr., Dept. of Radiology, Univ. of Chicago, 950 E. 59th St., Chicago 37, Ill. Meets second Thursday of each month, October to April except December at the Pick-Congress Hotel at 8:00 P.M.

Cleveland Radiological Society
Secretary-Treasurer, Dr. James Christie, 10515 Carnegie Avenue, Cleveland, Ohio. Meetings at 7:00 P.M. on fourth Monday of October, November, January, February, March and April.

Colorado Radiological Society
Secretary, Dr. David J. Stephenson, 8300 West 38th Ave., Wheat Ridge, Colo. Meets third Friday of each month at Denver Athletic Club from September through May.

*** Secretaries of societies are requested to send timely information promptly to the Editor.**

Connecticut Valley Radiologic Society
Secretary, Dr. William W. Walthall, Jr., 137 Maple St., Hartford 6, Conn. Meets in April and October.

Dallas-Fort Worth Radiological Society
Secretary, Dr. Paul W. Mathews, Jr., 1217 West Cannon St., Fort Worth, Tex. Meets monthly, third Monday, at Southwest International Airport at 6:00 P.M.

Detroit Roentgen Ray and Radium Society
Secretary, Dr. Arch H. Hall, Harper Hospital, Detroit 1, Mich. Meets monthly, first Thursday, October through May, at David Whitney House, 1010 Antietam, at 6:30 P.M.

East Bay Roentgen Society
Secretary, Dr. Dan Tucker, 434 30th St., Oakland 9, Calif. Meets first Thursday each month at Peralta Hospital, Oakland, Calif.

East Tennessee Radiological Society
Secretary, Dr. C. H. Kimball, 2200 Harris Circle, Cleveland, Tenn. Meets in January and September.

Eastern Radiological Society
Secretary, Dr. James F. Martin, North Carolina Baptist Hospital, Winston-Salem, N. C.

Florida Radiological Society
Secretary, Dr. Andre S. Capri, 3471 N. Federal Highway, Fort Lauderdale, Fla. Meets twice annually, in the spring with the annual State Society Meeting and in the fall.

Florida West Coast Radiological Society
Secretary-Treasurer, Dr. Garth R. Drewry, Tampa General Hospital, Tampa 6, Fla. Meets in January, April, July and October.

Georgia Radiological Society
Secretary, Dr. David Robinson, P.O. Box 394, Savannah, Ga. Meets in spring and fall with Annual State Society Meeting.

Greater Miami Radiological Society
Secretary-Treasurer, Dr. Oliver P. Winslow, Jr., Baptist Hospital of Miami, Inc., 8900 S. W. 88th St., Miami 56, Fla. Meets monthly, third Wednesday at 8:00 P.M. at Jackson Memorial Hospital, Miami, Fla.

Greater St. Louis Society of Radiologists
Secretary, Dr. C. M. Witt, #16 Hampton Village Plaza, St. Louis 9, Mo.

Houston Radiological Society
Secretary, Dr. D. A. Van Velzer, Texas Medical Center Library, Jesse H. Jones Library Bldg., Houston 25, Tex. Meets fourth Monday of each month, except June, July, August and December, at the Doctors' Club, 8:00 P.M., Houston, Tex.

Idaho State Radiological Society
Secretary, Dr. George H. Harris, Bannock Memorial Hospital, Pocatello, Idaho. Meets in the spring and fall.

Illinois Radiological Society
Secretary, Dr. George A. Miller, Carle Hospital Clinic, Urbana, Ill. Meets in the spring and fall.

Indiana Roentgen Society, Inc.
Secretary, Dr. Richard A. Silver, 1815 N. Capitol Avenue, Indianapolis, Ind. Meets first Sunday in May and during fall meeting of Indiana State Medical Association.

Iowa Radiological Society
Secretary, Dr. L. L. Maher, 1419 Woodland Ave., Des Moines, Iowa. Luncheon and business meeting during annual session of Iowa State Medical Society. The scientific section is held in the autumn.

Kansas Radiological Society
Secretary-Treasurer, Dr. R. F. Conrad, Newman Memorial Hospital, Emporia, Kan. Meets in spring with State Medical Society and in winter on call.

Kentucky Radiological Society
Secretary-Treasurer, Dr. Joan R. Hale, 402 Heyburn Building, Louisville, Ky. Meets monthly on second Friday at Sheraton Hotel, Louisville, Ky.

Kings County Radiological Society
Secretary, Dr. Stanley Dannenberg, 1917 Bedford Ave., Brooklyn 25, N. Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:45 P.M.

Knoxville Radiological Society
Secretary, Dr. Clifford L. Walton, Blount Professional Bldg., Knoxville 20, Tenn. Meetings are held the third Monday of every other month at the University of Tennessee Memorial Research Center and Hospital.

Los Angeles Radiological Society
Secretary, Dr. Austin R. Wilson, 540 N. Central Ave., Glendale, Calif. 91203. Meets second Wednesday of month in November, January, April and June at Los Angeles County Medical Association Building, Los Angeles, Calif. Annual midwinter meeting to be announced.

Maine Radiological Society
Secretary, Dr. J. T. Chen, 7 Cherry Hill Terrace, Waterville, Me. Meets in June, September, December and April.

Maryland Radiological Society
Secretary, Dr. Henry Startzman, Medical Arts Building, Baltimore, Maryland.

Memphis Roentgen Society
Secretary-Treasurer, Dr. Irving K. Ettman, 684 W. Brookhaven Circle, Memphis, Tenn. Meets first Monday of each month at John Gaston Hospital.

Miami Valley Radiological Society
Secretary, Dr. William D. Roberts, 2197 Los Arrow Dr., Dayton 9, Ohio. Meets second Friday of fall and winter months.

Mid-Hudson Radiological Society
Secretary-Treasurer, Dr. Alexander W. Friedman, Mid-Hudson Medical Group, Fishkill, N. Y. Meets 7:00 P.M., first Wednesday of each month September to May.

Milwaukee Roentgen Ray Society
Secretary-Treasurer, Dr. Harold F. Ibach, 2400 W. Villard Avenue, Milwaukee 9, Wis. Meets monthly on fourth Monday, October through May, at University Club.

Minnesota Radiological Society
Secretary-Treasurer, Dr. Frank J. Anderson, 810 E. 27th St., Minneapolis 7, Minn. Meets three times annually, in fall, winter and spring.

Mississippi Radiological Society
Secretary-Treasurer, Dr. Dan T. Keel, Jr., 504 Chippewa St., Brookhaven, Miss. Meets third Thursday of each month at the Heidelberg Hotel, Jackson, at 6:00 P.M.

Missouri Radiological Society
Secretary-Treasurer, Dr. M. Shoss, Cape Girardeau, Mo.

Montana Radiological Society
Secretary, Dr. Clark Grimm, Great Falls, Montana. Meets at least once a year.

Nassau Radiological Society
Secretary, Dr. Perry R. Mandel, Nassau Hospital, Mineola, L. I., N. Y. Meets second Tuesday of the month in February, April, June, October and December.

Nebraska State Radiological Society
Secretary, Dr. Richard Bunting, The Radiologic Center, Nebraska Methodist Hospital, Omaha 31, Neb. Meets third Wednesday of each month at 6 P.M. in Omaha or Lincoln.

Nevada Radiological Society
Secretary, Dr. William G. Arbonies, Department of Radiology, St. Mary's Hospital, Reno, Nev.

New England Roentgen Ray Society
Secretary, Dr. Jack R. Dreyfuss, Zero Emerson Place, Boston, Mass. 02114. Meets third Friday of each month, October through April, at The Longwood Towers, 20 Chapel Street, Brookline, Mass., at 4:30 P.M.

New Hampshire Roentgen Ray Society
Secretary, Dr. Paul Y. Hasserjian, 1470 Elm St., Manchester, N. H. Meets four to six times yearly.

New Mexico Association of Radiologists
Secretary-Treasurer, Dr. Justin J. Wolfson, Department of Radiology, Bernalillo County-Indian Hospital, Albuquerque, New Mexico.

New Mexico Society of Radiologists
Secretary, Dr. William G. McPheron, Hobbs, New Mexico. Four annual meetings, three held in Albuquerque, N. M., and one held at time and place of New Mexico State Medical Society annual meeting.

New Mexico Roentgen Society
Secretary, Dr. Harry Z. Mellins. Meets monthly on third

Monday at the New York Academy of Medicine at 4:30 P.M., Annual Spring Conference: Waldorf-Astoria Hotel, April 29, 30 and May 1, 1965.

North Carolina Radiological Society
Secretary, Dr. E. H. Schultz, North Carolina Memorial Hospital, Chapel Hill, N. C. Meets in the spring and fall each year.

North Dakota Radiological Society
Secretary, Dr. John Jestadt, Depuy-Sorkness Clinic, Jamestown, N. D. Meets at time of State Medical Association meeting. Other meetings arranged on call of the President.

North Florida Radiological Society
Secretary, Dr. Charles H. Newell, 800 Miami Road, Jacksonville 7, Fla. Meets quarterly in March, June, September and December.

Northeastern New York Radiological Society
Secretary, Dr. Anthony J. Tabacco, 621 Central Ave., Albany 6, N. Y. Meets in Albany area on second Wednesday of October, November, March and April.

Northern California Radiological Society
Secretary, Dr. John M. Johannessen, Mercy Hospital, Sacramento, Calif. Meets fourth Monday of Sept., Nov., Jan., March and May at the Sutter Club in Sacramento.

Northwestern Ohio Radiological Society
Secretary, Dr. Vito J. Zupa, Mercy Hospital, Department of Radiology, Toledo, Ohio.

Ohio State Radiological Society
Secretary, Dr. M. M. Thompson, Jr., 316 Michigan St., Toledo 2, Ohio. Annual meeting: Terrace Hilton Hotel, Cincinnati, Ohio, May, 1965.

Oklahoma State Radiological Society
Secretary, Dr. Dave B. Lhevine, B10 Doctors Bldg., 2021 South Lewis, Tulsa, Okla. Meets in January, May and October.

Orange County Radiological Society
Secretary-Treasurer, Dr. Robert M. Sodaro, 600 E. Washington Ave., Santa Ana, Calif. Meets fourth Tuesday of month except June, July, August and December in Orange County Medical Association Building.

Oregon Radiological Society
Secretary-Treasurer, Dr. James A. Schneider, St. Vincent Hospital, Portland 10, Ore. Meets on second Wednesday of month at 7:00 P.M. at the University Club, Portland, Ore

Orleans Parish Radiological Society
Secretary, Dr. Joseph V. Schlosser, Charity Hospital, New Orleans 13, La. Meets second Tuesday of each month.

Pacific Northwest Radiological Society
Secretary, Dr. Willis Taylor, Seattle, Washington. Annual meeting to be announced.

Pennsylvania Radiological Society
Secretary-Treasurer, Dr. Frederick R. Gilmore, Clearfield Hospital, Clearfield, Pa. Annual meeting: Pittsburgh Hilton Hotel, May 21–22, 1965.

Philadelphia Roentgen Ray Society
Secretary, Dr. Antolin Raventos, Hospital of the University of Pennsylvania, Philadelphia 4, Pa. Meets first Thursday of each month at 5 P.M., from October to May in Thompson Hall, College of Physicians.

Pittsburgh Roentgen Society
Secretary, Dr. Robert N. Berk, 3305 Fifth Ave., Pittsburgh 13, Pa. Meets second Wednesday of month, October through June at Park Schenely Restaurant.

Radiological Society of Connecticut
Secretary-Treasurer, Dr. Orlando F. Gabriele, 1450 Chapel St., New Haven 11, Conn. Meetings are held bimonthly.

Radiological Society of Greater Cincinnati
Secretary, Dr. John F. Popkin, Jr., 831 Carew Tower, Cincinnati, Ohio. Meets first Monday of each month at Cincinnati Academy of Medicine.

Radiological Society of Greater Kansas City
Secretary, Dr. J. Stewart Whitmore, 1010 Rialto Bldg., Kansas City, Mo. Meets last Friday of each month.

Radiological Society of Hawaii
Secretary, Dr. Russell E. Graf, P.O. Box 294, USA Tripler General Hospital, Honolulu, Hawaii. Meets third Monday of each month at 7:30 P.M.

Radiological Society of Kansas City
Secretary, Dr. Arthur B. Smith, 800 Argyle Bldg., Kansas City, Mo. Meets third Thursday of each month.

Radiological Society of Louisiana
Secretary, Dr. Andrew F. Giesen, Ochsner Clinic, New Orleans 15, La. Meets annually during Louisiana State Medical Society meeting.

Radiological Society of New Jersey
Secretary, Dr. E. Arthur Kratzman, 912 Prospect Ave., Plainfield, N. J. Meets in Atlantic City at time of State Medical Society meeting and in October or November in Newark, N. J.

Radiological Society of the State of New York
Secretary-Treasurer, Dr. John W. Colgan, 273 Hollywood Ave., Rochester 18, N. Y. Annual meeting to be announced.

Radiological Society of South Dakota
Secretary-Treasurer, Dr. Donald J. Peik, 303 S. Minnesota Ave., Sioux Falls, S. D.

Radiological Society of Southern California
Secretary-Treasurer, Dr. John L. Gwinn, Children's Hospital of Los Angeles, 4614 Sunset Blvd., Los Angeles, Calif. 90027. Meets three times a year, usually October, February, and May.

Redwood Empire Radiological Society
Secretary, Dr. Lee F. Titus, 164 W. Napa St., Sonoma, Calif. Meets second Monday every other month.

Richmond County Radiological Society
Secretary, Dr. W. F. Hamilton, Jr., University Hospital, Augusta, Ga. Meets first Thursday of each month at various hospitals.

Rochester Roentgen Ray Society, Rochester, N. Y.
Secretary, Dr. Gerald R. Holzwasser, Rochester General Hospital, Northside Division, 1425 Portland Ave., Rochester 21, N. Y. Meets at 8:15 P.M. on the last Monday of each month, September through May, at Strong Memorial Hospital.

Rocky Mountain Radiological Society
Secretary, Dr. John H. Freed, 4200 East Ninth Ave., Denver 20, Colo. Annual meeting to be announced.

San Antonio-Military Radiological Society
Secretary, Dr. Hugho F. Elmendorf, Jr., 730 Medical Arts Bldg., San Antonio 5, Tex. Meets third Wednesday each month in Fort Sam Houston Officer's Club at 6:30 P.M.

San Diego Radiological Society
President-Secretary, Charles P. Hyslop, 7901 Frost St., San Diego 22, Calif. Meets first Wednesday of each month at the University Club.

San Francisco Radiological Society
Secretary, Dr. Malcolm Jones, University of California Hospital, San Francisco 22, Calif. Meets quarterly at the San Francisco Medical Society, 250 Masonic Ave., San Francisco 18, Calif.

Section on Radiology, California Medical Association
Secretary, Dr. William H. Graham, 630 East Santa Clara St., San Jose, Calif.

Section on Radiology, Medical Society of the District of Columbia
Secretary-Treasurer, Dr. Martin A. Thomas, 1150 Connecticut Ave., Washington 36, D. C. Meets at Medical Society Library, third Wednesday of January, March, May and October at 8:00 P.M.

Section on Radiology, Southern Medical Association
Secretary,* Dr. John D. Reeves, Department of Radiology, Univ. of Florida College of Medicine, Gainesville, Fla. Annual meeting to be announced.

Section on Radiology, Texas Medical Association
Secretary, Dr. George F. Crawford, St. Elizabeth Hospital, Beaumont, Tex. Meets annually with the Texas Medical Association.

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* Deceased.

Shreveport Radiological Club
Secretary, W. R. Harwell, 608 Travis St., Shreveport, La. Meets monthly on third Wednesday at 7:30 P.M., September to May inclusive.

Society for Pediatric Radiology
Secretary, Dr. John L. Gwinn, Children's Hospital, Los Angeles 27, Calif. Annual meeting: Hilton Hotel, Washington, D. C., Sept. 27, 1965.

Society of Nuclear Medicine
Secretary, Mr. C. Craig Harris, Oak Ridge National Laboratories, Oak Ridge, Tenn. *Administrator*, Mr. Samuel N. Turiel, 430 N. Michigan Ave., Chicago 11, Ill. Annual meeting: Bal Harbour, Fla., June 16–19, 1965.

South Bay Radiological Society
Secretary, Northern Section: Dr. John H. Callaghan, 2900 Whipple Ave., Redwood City, Calif.; Southern Section: Dr. Paul L. Clemetson, 877 W. Fremont Ave., Suite C-3, Sunnyvale, Calif. Meets second Wednesday of each month.

South Carolina Radiological Society
Secretary, Dr. George W. Brunson, 1406 Gregg St., Columbia, S. C. Annual meeting (primarily business) in conjunction with the South Carolina Medical Association meeting in May. Annual fall scientific meeting at time and place designated by the president.

South Dakota Radiological Society
Secretary, Dr. Donald J. Peik, 1417 S. Minnesota Ave., Sioux Falls, S. Dak. Meets in spring with State Medical Society and in fall.

Southern Radiological Conference
Secretary-Treasurer, Dr. Marshall Eskridge, Mobile Infirmary, P.O. Box 4097, Mobile, Ala. Annual meeting to be announced.

Southwestern Radiological Society
Secretary, John M. McGuire, 904 Chelsea, El Paso, Tex. Meets last Monday of each month at 6:30 P.M. in the Paso del Norte Hotel.

Tennessee Radiological Society
Secretary, Dr. B. M. Brady, St. Joseph Hospital, Memphis, Tenn. Meets annually at the time and place of the Tennessee State Medical Association meeting.

Texas Radiological Society
Secretary, Dr. R. P. O'Bannon, 402 Professional Bldg., 1216 Pennsylvania Ave., Fort Worth 4, Tex. Annual meeting to be announced.

Tri-State Radiological Society
Secretary, Dr. John H. Marchand, Jr., Methodist Hospital, Henderson, Ky. Meets third Wednesday of Oct., Jan., March and May, 8:00 P.M., Elks Club in Evansville, Ind.

University of Michigan Department of Roentgenology Staff Meeting
Meets each Monday evening from September to June, at 7:00 P.M. at University Hospital, Ann Arbor, Mich.

Upper Peninsula Radiological Society
Secretary, Dr. A. Gonty, Menominee, Mich. Meets quarterly.

Utah State Radiological Society
Secretary, Dr. Carlisle C. Smith, Salt Lake General Hospital, Salt Lake City, Utah. Meets fourth Wednesday in January, March, May, September and November at Holy Cross Hospital.

Vermont Radiological Society
Secretary, Dr. John R. Williams, 160 Allen St., Rutland, Vt.

Virginia Radiological Society
Secretary, Dr. John M. Ratliff, Mary Immaculate Hospital, Newport News, Va.

Washington State Radiological Society
Secretary, Dr. Owen Marten, 930 Terry Avenue, Seattle, Wash. Meets quarterly.

West Virginia Radiological Society
Secretary, Dr. Karl J. Myers, The Myers Clinic-Broaddus Hospital, Philippi, W. Va. Meets concurrently with Annual Meeting of West Virginia State Medical Society; other meetings arranged by program committee.

Westchester Radiological Society
Secretary, Dr. Joel J. Schwartzman, Westchester Academy of Medicine, Section on Radiology, Purchase, N. Y. Meets on third Tuesday of January and October and on two other dates.

Wisconsin Radiological Society
Secretary, Dr. Charles Benkendorf, 408 St. Francis St., Green Bay, Wis. Meets twice a year, May and September

CUBA, MEXICO, PUERTO RICO AND CENTRAL AMERICA

Asociación de Radiólogos de Centro America y Panamá. Comprising: Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica and Panamá.
Secretary-General, Dr. Raul Arguello, 5a. Ave., Norte No. 48, San Salvador, El Salvador. Meets annually in a rotating manner in the six countries.

Sociedad de Radiología de El Salvador
Secretary, Dr. Rafael Vaga Gómez.

Sociedad de Radiología de Guatemala
Secretary, Dr. Carlos E. Escobar, 9ª. Calle A 0-05, Zona 1, Guatemala.

Sociedad de Radiología y Fisioterapía Cubana
Secretary, Dr. Miguel A. García Plasencia, Hospital Curie, 29 y F, Vedado, Habana, Cuba. Meets monthly at Curie Hospital.

Sociedad Costarricense de Radiologia
Secretary, Dr. James Fernández Carballo, Apartado VIII, San José, Costa Rica.

Sociedad Mexicana de Radiología, A.C.
Calle del Oro No. 15, México 7, D. F.
Secretary-General, Dr. E. Alvarez Hernández.
Meets first Monday of each month.

Asociación Puertorriqueña de Radiología
Secretary, Dr. R. B. Díaz Bonnet, Suite 504, Professional Bldg., Santurce, Puerto Rico.

Sociedad Radiológica Panameña
Secretary, Dr. L. Arrieta Sánchez, Apartado No. 6323, Panamá, R. de P. Meets monthly in a department of radiology of a local hospital chosen at preceding meeting.

Sociedad Radiológica de Puerto Rico
Secretary, Dr. Jorge Carreras Girard, Suite 504, Professional Bldg., Santurce, Puerto Rico. Meets second Thursday of each month at 8:00 P.M. at the Puerto Rico Medical Association Bldg. in San Juan.

BRITISH COMMONWEALTH OF NATIONS

Association of Radiologists of the Province of Quebec
Secretary, Dr. R. Robillard, Notre-Dame Hospital, 1560 Sherbrooke St., East, Montreal, Que., Canada. Meets four times a year.

British Institute of Radiology
Honorary Secretary, Dr. R. D. Hoare, 32 Welbeck St., London, W. 1, England. Meets monthly from October until May.

Canadian Association of Physicists, Division of Medical and Biological Physics.
Honorary Secretary-Treasurer, Paul M. Pfalzner, Dept. of Therapeutic Radiology, University of Western Ontario, London, Ont., Canada. Annual meeting: Toronto, Ontario, Feb., 1965.

Edmonton and District Radiological Society
Secretary, Dr. J. T. Mason, 540 Tegler Bldg., Edmonton, Alberta, Canada. Meets second Tuesday of each month, October to May.

Faculty of Radiologists
Honorary Secretary, Dr. J. N. Pattinson, 47 Lincoln's Inn Fields, London, W.C.2, England. Annual meeting: Cambridge, England, June 18–19, 1965.

Faculty of Radiologists, Royal College of Surgeons in Ireland
Registrar, Dr. H. O'Flanagan, F.R.C.P.I., D.P.H., 123 St. Stephens Green, Dublin 2, Ireland.

Section of Radiology of the Royal Society of Medicine (Confined to Medical Members)
Meets third Friday each month at 4:45 P.M. at the Royal Society of Medicine, 1 Wimpole St., London, W. 1, England.

Canadian Association of Radiologists

Honorary Secretary-Treasurer, Dr. D. J. Sieniewicz, *Associate Honorary Secretary-Treasurer*, Dr. Maurice Dufresne, 1555 Summerhill Ave., Montreal 25, Que., Canada. Annual meeting: Royal York Hotel, Toronto, Ontario, Feb., 24–28, 1965.

Montreal Radiological Study Club

Secretary, Dr. Leonard Rosenthall, Montreal General Hospital, Montreal, Que., Canada. Meets first Tuesday evening, October to April.

Section of Radiology, Canadian Medical Association

Secretary, Dr. C. M. Jones, Inglis St., Ext. Halifax, N. S.

Société Canadienne-Française d'Electro-Radiologie Médicale

General Secretary, Dr. Maurice Dufresne, 1560 Sherbrooke (East), Montreal, Que., Canada. Meets third Saturday each month.

Toronto Radiological Society

Secretary, Dr. Wallace M. Roy, St. Joseph's Hospitals, 30 The Queensway, Toronto 3, Ont., Canada. Meets second Monday of each month, September through May.

College of Radiologists of Australasia

Honorary Secretary, Dr. E. A. Booth, c/o British Medical Agency, 135 Macquarie St., Sydney, N.S.W., Australia.

South America

Asociación Argentina de Radiología

Secretary, Dr. Lidio G. Mosca, Avda. Gral. Paz 151, Córdoba, Argentina. Meetings held monthly.

Ateneo de Radiologia

Secretary, Dr. Victor A. Añaños, Instituto de Radiologia, Santa Fe 3100, Rosario, Argentina. Meets monthly on second and fourth Fridays at 7:00 p.m. in the Hospital Nacional de Centenario, Santa Fe 1300, Rosario.

Colégio Brasileiro de Radiologia

Secretary-General, Dr. Tede Eston de Eston, Caixa Postal 5984, São Paulo, Brazil.

Sociedad Argentina de Radiologia

Secretary, Dr. Armando B. de Onaindia, Santa Fe 1171, Buenos Aires. Meetings are held monthly.

Sociedad Bolivana de Radiología

Secretary, Dr. Javier Prada Méndez, Casilla 1596, La Paz, Bolivia. Meets monthly. General assembly once every two years.

Sociedade Brasileira de Radiologia

Secretary, Dr. Nicola Caminha, Av. Mem. de Sa, Rio de Janeiro, Brazil. General Assembly meets every two years in December.

Sociedade Brasileira de Radioterapia

Secretary, Dr. Oscar Rocha von Pfuhl, Av. Brigadeiro Luiz Antonio, 644, São Paulo, Brazil. Meets monthly on second Wednesday at 9:00 p.m. in São Paulo at Av. Brigadeiro Luiz Antonio, 644.

Sociedad Chilena de Radiología

Secretary, Dr. J. P. Velasco, Avenida Santa María 0410, Santiago, Chile. Meets fourth Friday of each month.

Sociedad Colombiana de Radiologia

Secretary, Dr. Armando Uribe, Hospital Miltar Central, Apartado aéreo No. 5804, Bogotá, Colombia. Meets last Thursday of each month.

Sociedad Ecuatoriana de Radiología y Fisioterapía

Secretary, Dr. Luis Blum, P.O. Box 3712, Guayaquil, Ecuador.

Sociedad Paraguaya de Radiología

Secretary, Dr. Miguel González Addone, 15 de Agosto 322, Asunción, Paraguay.

Sociedad Peruana de Radiologia

Secretary, Dr. Vicente Ubillus, Apartado 2306, Lima, Peru. Meets monthly except during January, February and March, at Asociación Médica Peruana "Daniel A. Carrión," Villalta 218, Lima.

Sociedad de Radiologica del Atlantico

Secretary, Dr. Raul Fernandez, Calle 40 #41–110, Baranquilla, Colombia. Society meets monthly at the Instituto de Radiologia.

Sociedad de Radiología, Cancerología y Física Médica del Uruguay

Secretary-General, Dr. Ernesto H. Cibils, Av. Agraciada 1464, piso 13, Montevideo, Uruguay.

Sociedade de Radiologia de Pernambuco

Secretary, Dr. Manoel Medeiros, Instituto de Radiologia da Faculdade de Medicina da Universidade do Recife, Caixa Postal 505, Pernambuco, Brazil.

Sociedad de Roentgenologia y Medicina Nuclear de la Provincia de Córdoba

Secretary-General Dr. Carlos A. Oulton, Santa Rosa 447, Córdoba, Argentina.

Sociedad Venezolana de Radiología

Secretary-General, Dr. Rubén Merenfeld, Apartado No. 9362 Candelaria, Caracas, Venezuela. Meets monthly third Friday at Colegio Médico del Distrito Federal, Caracas.

Continental Europe

Österreichische Röntgen-Gesellschaft

President, Dr. Konrad Weiss, Mariannengasse 10, Vienna 9, Austria. Meets second Tuesday of each month in Allgemeine Poliklinik. Annual meeting to be announced.

Société Belge de Radiologie

General Secretary, Prof. Simon Masy, Louvain, Belgium. Meets in February, March, May, June, September, October, November and December.

Société Européenne de Radiologie Pédiatrique

Permanent Secretary, Dr. Jaques Sauvegrain, Hôpital des Enfants-Malades, 149, rue de Sèvres, Paris 15e, France. *General Secretary*, Dr. Ole Eklöf, P.O. Box, Stockholm 60, Sweden. Annual meeting: Stockholm, Sweden, May 20–22, 1965.

Société Française d'Electroradiologie Médicale, and its branches: Société du Sud-Ouest, du Littoral Méditerranéen, du Centre et du Lyonnais, du Nord, de l'Ouest, de l'Est, et d'Alger et d'Afrique du Nord. Central Society meets third Monday of each month, except during July, August and September, rue de Seine 12, Paris, France.

Secretary-General, Dr. Ch. Proux, 9 rue Daru, Paris 8^{e}, France.

Československá Společnost pro Roentgenologii a Radiologii

Secretary, Dr. Robert Poch, Praha 12, Srobárova 50, Czechoslovakia. Meets monthly except during July, August, and September. Annual general meeting.

Deutsche Röntgengesellschaft

Secretary, Professor Dr. med. H. Lossen, Universitäts-Röntgeninstitut., Lagenbeckstr. 1, Mainz, Germany.

Società Italiana di Radiologia Medica e di Medicina Nucleare

Secretary, Dr. Ettore Conte, Ospedale Mauriziano, Torino, Italy. Meets annually.

Nederlandse Vereniging voor Radiologie

Secretary, Dr. H. F. O. Stricker, Schalklaar, Netherlands.

Scandinavian Roentgen Societies

The Scandinavian roentgen societies have formed a joint association called the Northern Association for Medical Radiology, meeting every second year in the different countries belonging to the Association.

Sociedad Española de Radiología y Electrología Médicas y Medicina Nuclear

Secretary, Dr. D. Aureo Gutierrez Churruca, Esparteros, No. 9, Madrid, Spain. Meets monthly in Madrid.

Schweizerische Gesellschaft für Radiologie und Nuklearmedizin (Société Suisse de Radiologie et de Médecine Nucléaire)

Secretary, Dr. Max Hopf, Effingerstrasse 47, Bern, Switzerland.

Asia

Indian Radiological Association

Secretary, Dr. R. F. Sethna, Navsari Building, Hornby Road, Bombay 1, India.

Indonesian Radiological Society

Secretary, Professor Sjahriar Rasad Taman Tjut Mutiah 1, Diakarta, Indonesia.

ABSTRACTS OF RADIOLOGICAL LITERATURE

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ROENTGEN DIAGNOSIS

Head

Fenner, Harold A., Jr. Football injuries and helmet design. *G.P.*, Oct., 1964, *30*, 106–113.

While the incidence of football fatalities is lower than that associated with firearms, swimming, and driving, the incidence of 1.5 per 100,000 exposures in high school and 2.5 per 100,000 exposures in college, as well as the steady rise in the percentage of head and neck injuries, with 16 of every 1,000 participants sustaining head, facial and neck injuries, is a cause for concern.

Injuries to the head and neck account for 72 per cent of all fatalities directly attributed to football. Neck injuries are secondary to flexion, hyperextension, lateral bending and torsional forces. Heads-up tackling and blocking are stressed for safety in order to see the opponent and to avoid danger, but this cannot be safely done when using helmets with large posterior slings or localized posterior padding which will impinge upon the back of the neck preventing a normal range of hyperextension. The inferior lateral edges of the helmet may cause damage to muscular and vascular structures by direct pressure, and to the spine by acting as a fulcrum laterally. This action may be enhanced by the addition of a tight narrow face bar which may compress the lower edges of the helmet. Irregularities on the external helmet surface may contribute to torsional injuries.

The severity of any given head injury reflects essentially the extent to which acceleration and deceleration forces are transmitted through the helmet to the skull and brain. Extensive testing has revealed that only 3 of the 16 major brand helmets provide an adequate degree of protection. The leather type of helmet has very poor protective qualities. The less rigid plastic shells are easily indented such that the impacting force is directly transmitted to the calvarium and then this soft shell rebounds and no external hint of damage is detected. The internal sling of the helmet offers some protection from blows to the vertex, but this protection fails with blows at or below the lower level of the sling with result that the blow may be transmitted directly to the head. The sling and padding posteriorly cause undue stress upon the cervical structures even within the limits of normal hyperextension.

The greatest protection would appear to be offered by an extremely rigid but light outer shell such as can be afforded by fiber glass which is used in combination with an inner liner of nonresilient or crushable material of foamed plastic which has high energy-absorbing properties. Added to this prototype helmet was a slow-rebound comfort liner overlaid by a fabric cover and supplemented by rubber edge protection, and cheek and sizing pads. Dynamic testing revealed a marked improvement in the attenuation of transmission of the impact forces to the head, with a considerable subjective improvement as compared with the old type sling helmets. The prototype helmet was considered to be more comfortable, it did not impinge on the shoulder pads and back of the neck when the player assumed the football stance; only 15 per cent had postcontact headaches as compared with 95 per cent of the players wearing the standard helmets; and only 2 of 61 players who had previously experienced momentary periods of disorientation immediately after heavy contact experienced this same sensation with the new helmet. A helmet consisting of a plastic shell, nonresilient liner and a sling suspension was recently tested. It performed better than the standard football helmet but did not perform nearly as well as the nonsling prototype.

It is recommended that the sale of plastic shells for small children should also be completely eliminated as these helmets are inadequate protection not only in football, but also in soapbox derbies, go-cart racing, and baseball.—*Donald M. Monson, M.D.*

Levin, Philip, Gross, Sidney W., Malis, Leonard I., Kirshenbaum, A. Hyman, and Hollin, Sidney A. Multiple intracranial meningiomas. *Surg., Gynec. & Obst.*, Nov., 1964, *119*, 1085–1090. (From: Departments of Neurosurgery, The Mount Sinai Hospital, New York, and The City Hospital Center at Elmhurst, New York, N.Y.)

Six cases of multiple intracranial meningiomas are reported. "Multiple meningioma" denotes the occurrence of more than one intracranial meningioma at one time. Excluded are diffuse meningiomas and recurrent meningiomas. Multiple meningiomas are known to occur also with centralized neurofibromatosis and acoustic nerve tumors.

Multiple meningiomas are observed in 1 to 6.7 per cent of patients with meningiomas. Both ectodermal and mesodermal origins have been postulated for the meninges; the arachnoid granulations and randomly scattered endothelial cells are the theoretic sources of meningiomas.

Multicentric foci, spread along cerebrospinal fluid pathways and venous transmission are possible explanations for the multiplicity of meningiomas. Acoustic nerve tumors in Recklinghausen's disease, retinoblastoma, and hemangioblastoma arise from multicentric foci; meduloblastomas are known to be transmitted by cerebral spinal fluid pathways; extracranial metastases in the lungs, pleura, mediastinum, and liver constitute evidence for the entry of neoplastic cells into the venous pathways. Meningiomas occurring rostral to the original tumor may be due to altered blood flow in the longitudinal sinus.

Skull roentgenograms may show areas of hyperostosis or enlargement of the middle meningeal artery grooves. Arteriography of the internal and external carotid systems has brought attention to the meningeal vessels, which may be enlarged due to increased blood flow. The artery of Bernasconi and Cassinari reportedly is commonly seen in tentorial meningiomas. Roentgenographic illustrations of these vessels as visualized at cerebral angiography, as well as pneumoencephalographic findings are included in the discussion.—*John T. Underberg, M.D.*

NATHAN, ALVIS S. Ameloblastoma. *Bull. Hosp. Joint Dis.*, Oct., 1963, *24*, 153–166. (Address: Clinical Professor in Dentistry [Oral Surgery], Columbia University, New York, N.Y.)

A slow growing tumor, ameloblastoma, arises from dental epithelium and is found in the mandible at the angle of the jaw or in the molar region and occasionally in the maxilla. Young adult males are most frequently affected. Basically it is a benign lesion, which invades adjacent bone and may recur if not radically excised. Rarely this histologic picture is seen in a tumor in a long bone such as the tibia.

Differential diagnosis includes the giant cell reparative granuloma, the central giant cell tumor, lesions of hyperparathyroidism, fibrous dysplasia, and histiocytosis.

Description of the gross tumors and histologic patterns are given and the classification into a gingival, medullary, follicular, and carcinomatous type is reviewed.

Two cases are presented in detail with excellent histologic and roentgenographic reproductions.

The author comments on the methods of treatment while favoring the conservative approach.—*David C. Alftine, M.D.*

STECKER, RAYMOND H., DEVINE, KENNETH D., and HARRISON, EDGAR G., JR. Verrucose "snuff dipper's" carcinoma of the oral cavity: a case of self-induced carcinogenesis. *J.A.M.A.*, Sept. 14, 1964, *189*, 838–840. (Address: Capt. Stecker, Mayo Clinic, Rochester, Minn. 55901.)

A case of verrucose, squamous carcinoma of the posterior surface of the lower lip is reported, where the association with a long history of snuff dipping is well documented.

From 1935 through 1957, 55 patients with verrucose, squamous carcinoma of the oral cavity were treated at the Mayo Clinic. The lesions were typically Grade I carcinomas, without lymph node or distant metastases, large and invading by local contiguous spread.

Wide local removal without dissection of the neck should be sufficient to control this tumor.— *John Antoniades, M.D.*

NECK AND CHEST

ROSSI, P., SABOT, G., and VIDAL, B. Sulla tracheobroncomegalia (Sindrome di Mounier-Kuhn). (Tracheobronchiomegaly—Mounier-Kuhn syndrome.) *Radiol. med.*, July, 1964, *50*, 623–632. (Address: Dott. Paolo Rossi, Via Cormor Alto, 28, Udine, Italy.)

Tracheobronchiomegaly is a rare disease characterized by a marked dilatation of the trachea and major bronchi complicated by chronic inflammatory processes of the bronchial tree.

This syndrome has been also called: trachealectasia, tracheomalacia, idiopathic megatrachea and malacic tracheobronchopathy. The authors feel that the term malacia should not be used since in tracheobronchiomegaly there is no softening or partial disappearance of the cartilaginous rings, even in a circumscribed segment of the trachea.

The etiology is not as yet clarified but the majority of the authors believe that tracheobronchiomegaly is due to a congenital abnormality in the elastic and muscular fibers of the tracheobronchial tree. It is generally agreed that the inflammatory complications should be considered an important aggravating factor.

The symptoms are not characteristic and the disease presents clinical findings related to the chronic inflammatory processes involving the parenchyma and bronchi.

On bronchoscopy, the lumen of the trachea and major bronchi is markedly dilated, with saccular dilatation of the membranous rings and short stenotic segments in the trachea. The mucosa is edematous and hyperemic.

In the standard roentgenogram of the chest one notes an abnormal dilatation of the trachea, usually associated with emphysema, pulmonary fibrosis, bullae, etc. Tomography demonstrates clearly the changes in the walls of the trachea and major bronchi. Bronchography shows a typical pattern, which the authors compare to that of a dilated loop of bowel with marked visualization of the intestinal glands; this is due to contrast medium being retained in the plicae of the trachea.

Under fluoroscopic observation it is possible to note that a Valsalva maneuver produces an increase of the lumen of the trachea, while in the Müller maneuver there is a narrowing of the lumen.

The case reported is that of a man of 59 years of age who for 10 years had recurrent episodes of bronchopneumonic processes. The bronchoscopic and bronchographic findings were typical of the syndrome.—*A. F. Govoni, M.D.*

CRAWFORD, STANLEY E. Histoplasmosis in infants and children. *G. P.*, Sept., 1964, *30*, 78–85. (From: Department of Pediatrics, University of Tennessee College of Medicine, Memphis, Tenn.)

Histoplasma capsulatum is estimated to affect 90 per cent of the population in endemic areas. The organism is found in soil and has been isolated from the droppings of bats, starlings, pigeons, chickens, blackbirds, etc. The fungus also has been isolated in abundance from the dust of attics, barns, chicken coops and dirt excavations. Transmission from man to man or animal to man apparently does not occur. Cultures can be grown on routine laboratory media.

The skin test may be compared with that for tuberculosis, since it indicates old or recent infections but does not define activity. There are four serologic tests for this disease.

The diagnosis is based on the skin test, the roentgenogram, the serologic data and the culture or identification of the organism.

Infections caused by this organism may be classified in the following manner: (1) inapparent infection without illness; (2) mild pulmonary histoplasmosis; and (3) moderately severe pulmonary disease. The first two require no treatment. The latter usually is protracted, and is benefited by sulfonamides. Other forms of the disease include: (4) epidemic histoplasmosis; (5) chronic pulmonary disease with cavitation. This form of histoplasmosis is usually observed in adults. Apical pulmonary lesions are noted and sputum cultures often recover the organism. There is a real danger of blood stream dissemination; (6) coexisting histoplasmosis and tuberculosis. This condition is rare in children but does occur. A high incidence, about 25 per cent of active tuberculosis, has been reported in adults with chronic pulmonary histoplasmosis; (7) acute disseminated histoplasmosis; (8) unusual forms including myocarditis and pericarditis have been reported. Any organ of the body may become infected with this organism.

The author discusses the treatment and the use of several drugs with indications on the basis of dissemination and severity of the infection.—*David C. Alftine, M.D.*

VILLA-VENZANO, G., and DE LUCA, G. Il quadro radiologico polmonare nel rachitismo. (The pulmonary radiologic picture in rickets.) *Radiol. med.*, June, 1964, *50*, 534–545. (Address: Dott. Giorgio De Luca, Via Fieschi, 6, Genova, Italy.)

Fifty children of ages from 3 months to 6 years, all affected by avitaminosis D in active stage, were observed by the authors; 39 of them presented pulmonary lesions.

The most important roentgenologic findings were: skeletal changes due to rickets, 100 per cent; abnormal visibility of the trachea, 10 per cent; plate-like atelectases, 39 per cent; diffuse emphysema, 37 per cent; apical emphysema, 31 per cent; and basal emphysema 28 per cent.

The abnormal visualization of the trachea and major bronchi is related to the deficiency of calcium of the skeletal system, resulting in a secondary diminished radiopacity.

The plate-like atelectases and circumscribed areas of emphysema are believed by some authors to be the result of stasis due to impaired respiratory dynamics, or compression of the parenchyma produced by the morphologic alterations in the thoracic cage.

Other investigators feel that the pathologic changes in the lungs are secondary to degeneration of the elastic fibers and the structural lesions, affecting the perichondrium and the chondral layers of the bronchi.

Several cases are reported in detail.—*A. F. Govoni, M.D.*

SAUTTER, R. D., FLETCHER, F. W., EMANUEL, D. A., LAWTON, B. R., and OLSEN, T. G. Complete resolution of massive pulmonary thromboembolism. *J.A.M.A.*, Sept. 21, 1964, *189*, 948–949. (Address: Dr. Sautter, Marshfield Clinic, Marshfield, Wis.)

The authors report 2 cases of so-called massive pulmonary thromboembolism documented by pulmonary arteriography which showed complete resolution. The cases were among 8 diagnosed in a period of 3 years. Pulmonary embolectomy was performed or attempted in 6 of the patients; 2 patients survived. Two cases reported did not have surgical embolectomy because of satisfactory clinical condition in spite of the emboli. Both patients were treated with inferior vena cava ligation and anticoagulation therapy. No specific medications other than the anticoagulant therapy was given and it is assumed that the patient's own fibrinolytic system caused the resolution of the emboli.

Before and after pulmonary arteriograms are included to accompany the first case. The interpretation is not clear because the phases of the pulmonary circulation and projections are different.—*Donald S. Linton, Jr., M.D.*

HOLMES, R. BRIAN, and MACFADYEN, L. R. Aneurysms of the heart. *J. Canad. A. Radiologists*, Sept., 1964, *15*, 110–117. (From: Toronto General Hospital, Toronto, Ontario.)

Cardiac aneurysms are relatively common in patients with a history of myocardial infarction, the reported incidence being 12 to 20 per cent in some series. However, they may occur in any disease producing a localized weakening of the wall; they have been described in association with septic emboli, ulcerative endocarditis, rheumatic necrosis, gumma, and trauma.

The ventricular bulge may develop within 2 days or perhaps not for several years, and its size may remain stationary or enlarge, the eventual size depending upon the area of weakened myocardium.

Cardiac aneurysms most frequently involve the left ventricle, particularly its anterolateral and apical aspect. Often mural thrombosis is found within the aneurysmal cavity. Pericardial adhesions tend to form over its surface and calcification may appear within its wall.

Left ventricular aneurysms do not present any specific symptomatology and their presence is frequently not suspected. Occasionally, a double apical impulse can be felt. The diagnosis is most commonly made roentgenologically. Plain roentgenograms may be normal but usually the heart is enlarged, predominantly the left ventricle. A localized bulge of the left ventricle, particularly if it contains calcium, is practically pathognomonic. Fluoroscopy is the best method for preliminary assessment, especially when coupled with image intensification and cine recording. Because of its usual position, it is best seen in posteroanterior or slight anterior oblique projections. Pulsation is characteristically paradoxical with expansion of the aneurysmal chamber during ventricular systole. The size of the aneurysmal chamber and the associated hemodynamics can be demonstrated by opacification of the left ventricle either by selective injection or via the venous route.

The prognosis varies greatly depending upon the size and location of the aneurysm, the degree of coronary artery disease and the state of the myocardium. Rupture of the aneurysm almost always occurred during the 2 weeks following myocardial infarction. The cause of death, in the majority of cases, was related to the progress of the associated coronary artery disease. However, in some, there is elevation of the ventricular end diastolic pressure caused by a combination of the useless flow of blood in and out of the aneurysm and the diminished compliance due to the failure of the aneurysm to expand along with the rest of the ventricle during diastolic filling. This added strain on the already jeopardized myocardium may be sufficient to induce left ventricular failure.

Surgical removal of the aneurysm has been beneficial in some cases, although the followup has been too short to assess ultimate prognosis. When combined with catheter data, the roentgenologic findings help to indicate those patients who would be likely to benefit from surgical removal of the aneurysm.—*Alan G. Greene, M.D.*

Hussain, R. (Blackpool, England.) Oesophageal stricture following use of indwelling Ryle's tube. *Brit. J. Surg.*, July, 1964, *51*, 525–527.

The author reports 2 cases of esophageal stricture following the use of Ryle's tube in the postoperative management of surgical patients.

A discussion as to the basic etiologic factors involved suggests that vomiting causes a form of "mechanical scouring" to the esophageal mucous membrane, thereby making it more vulnerable to further trauma by the Ryle's tube. Poor nutrition, general debilitation and old age are thought to be contributing factors. Finally, the presence of esophageal hiatal hernia with associated esophageal reflux and subsequent esophagitis, is felt to play a major role in the production of stricture formation.

In the cases presented, both patients were found to have hiatal hernias. Esophagoscopy and tissue diagnoses were obtained prior to treatment.—*Donald S. Faust, M.D.*

Larson, Norman E., Larson, Richard H., and Dorsey, John M. Mechanism of obstruction and strangulation in hernias of the esophageal hiatus. *Surg., Gynec. & Obst.*, Oct., 1964, *119*, 835–841. (From: Department of Surgery, Northwestern University Medical School, Chicago, and Evanston Hospital, Evanston, Ill.)

Obstruction of a segment of intestine or stomach in a diaphragmatic hernia has a high mortality rate in untreated cases. In some series, 80–90 per cent of these hernias were traumatic in nature. In other series the complications arose with esophageal hiatus hernias, and with the "upside down" thoracic stomach in which obstruction developed after the proximal portion of the stomach had returned into the abdomen.

The authors deal only with the paraesophageal hiatal hernia in which the defect in the diaphragm is located anterolateral to the esophageal hiatus.

Two cases of gastric obstruction in paraesophageal hiatal hernia are presented and a series of drawings is used to illustrate the mechanism of obstruction and strangulation in this type of hernia. It is pointed out that this is a progressive condition, and a more aggressive surgical approach is needed in some cases. —*Richard E. Kinzer, M.D.*

ABDOMEN

Ambert, John R., Ellison, Edwin H., Wilson, Stuart D., and Zboralske, F. Frank. Roentgenographic observations in the Zollinger-Ellison syndrome. *J.A.M.A.*, Oct. 19, 1964, *190*, 185–187. (From: Divisions of Radiology and Surgery, Marquette University School of Medicine, Milwaukee, Wis.)

This is a most succinct and informative article regarding a relatively new, little appreciated syndrome; it is recommended for the straightforward simplicity of its literary style and its medical content.

The pathologic physiology of Zollinger-Ellison syndrome is described briefly, but as completely as present knowledge will permit.

The morphologic changes in the gastrointestinal tract are reflected roentgenographically sufficiently often to suggest the Zollinger-Ellison syndrome preoperatively.

The roentgenographic findings consist of a dilated, fluid filled stomach, in spite of 12-hour fasting and in the absence of an obstructive phenomenon; decreased gastric peristalsis; large gastric folds; and occasional gastric ulceration.

The commonest finding is duodenal ulcer (75 per cent of cases) and megaloduodenum. Ulcers immediately beyond the bulb increase the probability of ulcerogenic tumor of the duodenum (Zollinger-Ellison syndrome). Ulceration in the jejunum is almost pathognomonic of this disease.

Small bowel changes include hypermotility and edema of the mucosal pattern.

Suspicious roentgenographic findings should lead to studies of gastric secretion and proper surgical therapy. When the total volume of a 12-hour overnight collection of gastric secretion exceeds 2,100 cc. and contains over 100 mEq. of free HCl, the diagnosis of Zollinger-Ellison syndrome is likely.

Total gastrectomy is the treatment of choice.—*John H. Harris, M.D.*

Schwartz, Donald R., and Wirka, H. W. The cast syndrome: a case report and discussion of the literature. *J. Bone & Joint Surg.*, Oct., 1964, *46A*, 1549–1552. (Address: Dr. Schwartz, United States Air Force Hospital, Travis Air Force Base, Fairfield, Calif.)

The cast syndrome is defined as acute duodenal obstruction following application of a body cast. This condition was first reported in 1878. Subsequent theories as to the mechanism of obstruction include pressure of the mesenteric and superior mesenteric vessels on the duodenum as they cross the spine, reflex atonia with failure of resorption of gastric and pancreatic juice, and air swallowing due to relaxation of the superior esophageal sphincter.

Surgical exploration was performed in 2 cases previously reported. In one patient definite arteriomesenteric occlusion of the duodenum was found. In the second case no definite point of obstruction of the dilated duodenum was discovered; however, the bowel appeared normal below the ligament of Treitz and following surgery on this ligament the patient slowly recovered.

The authors report the case of a 15 year old boy with severe paralytic scoliosis and associated marked lumbar lordosis. Severe atony of the abdominal musculature was also present. Following spinal fusion, the patient was placed in a body cast. Shortly thereafter, symptoms of duodenal obstruction became evident. An upper gastrointestinal series revealed almost complete duodenal obstruction. On subsequent surgery a markedly distended duodenum was found proximal to the superior mesenteric vessels. These vessels were taut and compressed against the lordotic spine. A duodenojejunostomy was performed with eventual recovery.

Traction of the mesenteric vessels was believed to be due to laxity of the abdominal muscles, thus allowing the bowel to descend into the pelvis, placing stretch on the mesenteric vessels with compression against the markedly lordotic lumbar spine.

Early diagnosis of this entity by barium swallow study is urged in view of the dire consequences attending unrecognized duodenal obstruction.—*E. Arnoldi, M.D.*

Rosen, Irving B., and Shapiro, Bernard J. Radiation enteropathy of the small bowel. *Canad. M. A. J.*, Sept. 26, 1964, *91*, 681–688. (From: Departments of Surgery and Radiology, New Mount Sinai Hospital, Toronto, Ontario, Canada.)

Gynecologic cancer and, in particular, carcinoma of the cervix uteri are commonly treated by irradiation. The quite successful management of cervix cancer in this manner is attended with considerable morbidity due to radiation injuries of all the adjacent structures, including especially the urinary bladder and ureters, the rectum, and other parts of the gastrointestinal tract.

Since the small bowel does not normally have a fixed position with reference to the pelvic structures, it usually escapes injury, but the authors wish to point out that in a large gynecologic service a significant number of women are seen with radiation-injured small bowel, presenting real clinical problems. The features of radiation injury of the small bowel are described and 3 cases are reported for illustration.

Chronic ulcer may evolve over a period of 6 months to several years. The involved small bowel is usually adherent in the pelvis. Bacterial infection commonly occurs, and perforation and gangrene are not uncommon.

The case presentations illustrate obstruction, fistula formation, and perforation; the surgical and medical management is discussed.—*Richard E. Kinzer, M.D.*

DiCenso, Sabatino, Ginsburg, Samuel B., and Snyder, William H., Jr. Pancreatic pseudocysts in childhood. *Surg., Gynec. &*

Obst., Nov., 1964, *119*, 1049–1052. (From: Department of Surgery, Children's Hospital of Los Angeles, and the University of Southern California, School of Medicine, Los Angeles, Calif.)

Four case reports of a rare childhood entity, pancreatic pseudocysts, are presented with accompanying illustrations.

A pancreatic pseudocyst is characterized by a fibrous lining and may be classified as: post inflammatory, post traumatic, neoplastic, parasitic, or idiopathic. It must be distinguished from a true cyst in which an epithelial lining is present. Pancreatic pseudocysts are most commonly the result of trauma or pancreatitis—the former in children and the latter in adults.

Abdominal pain or fullness, nausea, vomiting, and weight loss are the presenting symptoms. An abdominal mass is usually palpable. Roentgenologic studies are helpful in locating the position of the mass. The serum amylase value is normal; at laparotomy marked elevation of the cyst fluid amylase level indicates the pancreatic origin of the mass. Choledochal, renal, mesenteric, and omental cysts must be differentiated from pancreatic pseudocysts.

Treatment consists of excision or drainage. Excision in adults may lead to external pancreatic fistula formation. External drainage is associated with a higher recurrence rate and excess fluid and electrolyte loss. Internal drainage by cyst gastrostomy, cyst duodenostomy, or cyst jejunostomy is preferred.—*John T. Underberg, M.D.*

Chapman, M., Curry, R. C., and Le Quesne, L. P. Operative cholangiography: an assessment of its reliability in the diagnosis of a normal, stone-free common bile-duct. *Brit. J. Surg.*, Aug., 1964, *51*, 600–601. (From: Department of Surgical Studies and the Department of X-ray Diagnosis, The Middlesex Hospital, London, England.)

Ninety patients had cholecystectomies 12 or more months preceding this study. All had one or more stones in the gallbladder at surgery.

Operative cholangiography was done at surgery to determine the need for exploration of the common duct. Exploration of the duct was not done if the following criteria were met, as interpreted from the roentgenogram: (1) a duct of normal caliber, a diameter of 14 mm., as measured on the cholangiogram, being taken as representing the upper limit of normal; (2) free flow of opaque medium into the duodenum apparent on all cholangiograms; (3) the terminal narrow segment of the duct, with the characteristic notch at its junction with the wider proximal portion, clearly seen in at least one cholangiogram; (4) absence of filling defect; and (5) no excess retrograde filling of the intrahepatic radicles.

At follow-up, each patient was interviewed in detail and note was taken of the course since surgery. In addition, intravenous cholangiography was performed and the films were studied. In no patient did this follow-up show clinical or roentgenographic evidence of residual stone in the common duct.

The authors conclude that a normal operative cholangiogram can be relied on as evidence that the common duct is stone-free.—*David C. Alftine, M.D.*

GYNECOLOGY AND OBSTETRICS

Bevis, D.C.A. Diagnosis of placenta praevia by angiography: obstetrical aspects. *Proc. Roy. Soc. Med.*, Aug., 1964, *57*, 700–702. (From: Park Hospital, Davyhulme, Manchester, England.)

Before 1947 when placenta previa was diagnosed it was usual to deliver the child as soon as was practicable after the initial hemorrhage. The fetal mortality was about 60 per cent and the maternal mortality about 6 per cent. Efforts were then made to postpone delivery by prolonging the pregnancy until the risks of prematurity were passed, usually to the 35th or 36th week, with a decline in the fetal mortality to roughly 5 per cent. But the condition remains a danger, as can be seen from the figures of the Ministry of Health Report on Maternal Deaths of 742 deaths in the years 1958–1960; 130 were due to hemorrhage in all its forms and 25 of these were due to placenta previa; moreover 19 of these were avoidable.

Naturally many difficulties arise in such a method of treatment and not the least is the problem of keeping the patient in hospital for anything up to 2 months when for most, if not all, of this time she is perfectly well. However, the danger with placenta previa is that the initial hemorrhage is rarely the most lethal to the mother and it is essential for patients with this condition to remain in hospital so that prompt treatment can be undertaken should they have further bleeding.

The only certain way of establishing the diagnosis of placenta previa clinically is to pass a finger through the cervix to palpate the lower uterine segment. This does not always require anesthesia but it is liable to induce labor or further bleeding and is therefore avoided for as long as possible, until a formal examination is made in the operating theater before delivery of the child. On admission, a provisional diagnosis is made and the patient kept in hospital until the child is of a reasonable size, preferably until the 36th week.

The main value of angiography is that it enables the site of the placenta to be accurately determined early enough in pregnancy for the obstetrician to divide his patients into those who must be advised to stay in hospital until the later weeks of pregnancy and those who may safely be allowed home under the care of the antenatal clinic. The roentgenologic hazards of the procedure are slight and the examination can be carried out at any time after the 28th week of pregnancy.

This method of demonstrating the placental site has resulted in a much more logical treatment of patients with antepartum hemorrhage with better outlook for the fetus, better use of antenatal beds and, most important, more contented patients.—*Eugene J. McDonald, M.D.*

Ainsworth, J., and Gilman, P. W. (Manchester, England.) Diagnosis of placenta praevia by aortography. *Proc. Roy. Soc. Med.*, Aug., 1964, *57*, 697–700.

In expert hands and with high quality roentgenograms it is possible, using the soft tissue method, to demonstrate the placental site with accuracy in 90–95 per cent of cases. This method of placental localization in less expert hands may, however, fail unless all factors are favorable and it is often in just such a case that placental localization is required.

Arteriography permits an accurate localization of the placental site at any stage of pregnancy and irrespective of the presentation of the fetus or presence of hydramnios. A 7F teflon catheter is positioned so that it lies at the level of the bifurcation of the aorta. The position of the tip of the catheter is important, since the placenta is often supplied mainly by one uterine artery, and unless both iliac arteries, and hence both uterine arteries, are filled with the contrast medium the placenta may not be seen. The injection of 30 ml. of 60 per cent sodium diatrizoate is made either by hand pressure or by using a compressed air injection pump, the injection time being about 2 seconds. This slow injection is necessary to ensure that the opaque medium flows through the uterine arteries for a reasonable period, in order that the placental sinuses may fill adequately. A delay of 2 seconds is then allowed and a single anteroposterior roentgenogram is taken, using a 17×14 inch film, to include the whole of the uterus.

The roentgenogram is examined before withdrawal of the catheter and if necessary a second injection is made and a roentgenogram obtained in the lateral projection. When the roentgenograms are judged to be satisfactory the catheter is withdrawn.

The hazards of the examination appear to be no greater and probably less than in normal retrograde aortography, since the vessels utilized are those of a healthy young adult unlike the diseased vessels in older patients which are often encountered in routine retrograde aortographic examination. The study should not be performed if there is severe renal or hepatic damage; nor in the patient in shock where the low blood pressure may allow large quantities of the opaque medium to reach the renal circulation with consequent risk of renal damage. The authors never opacified the fetal circulation and it is probable that such transference of the opaque medium is only slow and slight.

The uterine arteries are easily seen and have a width of about twice that seen in the nonpregnant patient. The main trunk of the uterine artery is visualized in the parametrium running more or less transversely and in this portion it may be either straight or tortuous. It then runs vertically upwards in the lateral wall of the uterus, and is quite straight in this portion. As it approaches the placental site, it branches into the small vessels which become increasingly tortuous and have a corkscrew-like appearance as the placental site is reached. Very often the main blood supply to the placenta appears to originate from one uterine artery; hence, the importance in ensuring that both uterine arteries are adequately filled by the opaque material.

Placental sinuses are easily identified as irregular mottled opacities, sometimes with confluent outlines which remain filled with the opaque medium usually for several seconds. Sometimes these opacities may have a clear central area giving a rosette-like appearance and this is thought to be due to discharge of a jet of blood not containing any opaque medium into the center of the opacified sinus. This appearance is in accordance with the theory of the jet discharge of the branches of the uterine artery into the placental sinuses. In some cases the veins in the vicinity of the placenta are shown; these are usually small and curved, and occasionally a curved opacity in the uterine wall is seen which is thought to represent a marginal sinus.

The placental site has been shown to lie in any position within the uterus. When the placenta is shown to lie in the upper portion of the uterus on the initial roentgenograms, the examination is discontinued, for only in exceptional circumstances is accurate localization of practical importance when placenta previa has been excluded. If the lower margin of the placenta appears to lie within the true pelvis, the presence of some degree of placenta previa is suspected and a further attempt at localization is made by means of a lateral roentgenogram. This clearly shows whether the placenta is lying on the anterior or posterior wall of the uterus and the presence of a placenta previa can be estimated. Minor degrees of placenta previa may be difficult to estimate, owing to the difficulty of determining the exact boundaries of the lower segment of the uterus. It appears that, if the lower margin of the placenta lies more than 10 cm. from the external os, placenta previa can be excluded.

Sixty-one cases of antepartum hemorrhage have been examined by this method. In 60 cases adequate visualization of the placenta was obtained, in the remaining case the placenta was not shown. This patient was at term and nonvisualization was thought to be due to uterine contractions. In 48 cases placenta previa was excluded, correctly, as follow-up confirmed.—*Eugene J. McDonald, M.D.*

Samuel, Eric. The inferior vena cavogram in pregnancy: radiological aspects. *Proc. Roy. Soc. Med.*, Aug., 1964, *57*, 702–705. (From: Royal Infirmary, Edinburgh, Scotland.)

To investigate the cause for the raised pressure in the inferior vena cava, it was decided to perform inferior vena cavography. At first, because of the possibility of radiation hazards, it was only performed on patients with fetal abnormalities and then only immediately before the termination of pregnancy.

A 160 polythene catheter was introduced into each femoral vein by the Seldinger method of percutaneous puncture and the catheter passed along the vein for approximately 13 cm. to get beyond the origin of the internal iliac veins. In later examinations the catheters were not inserted so far. Both catheters were connected to a Y-tube which was attached to a hand syringe. Twenty ml. of 60 per cent sodium diatrizoate was injected under hand pressure and serial films were exposed half-way through and at the end of the injection.

Later it was judged important to find if the abnormal flow noted was entirely due to uterine pressure on the vena cava. Patients who were to have elective cesarean section were investigated. Consequently, with the patient lying on a cassette changing tunnel placed on the operating table, anesthesia was induced and both femoral veins were punctured by the method described. A single film was immediately exposed at the end of injection. Elective cesarean section was then performed with the catheters left *in situ* in the femoral veins, intermittent saline perfusion being carried out to keep the catheters clear. When the uterus had been repaired, it was held forward by two long catgut sutures and a repeat injection of 20 ml. of 60 per cent sodium diatrizoate was made. The pre- and post-cesarean films were compared. The roentgenographic quality of the films was naturally inferior to that obtained on the larger units in the X-ray department, but was adequate for diagnostic purposes.

Normally, the inferior vena cava shows little filling of its tributaries and is seen to extend as a smooth column with some indentation from the renal artery and right common iliac artery. Slight reflux of opaque material into the renal veins may be seen.

In pregnancy a vastly different appearance was noted. The inferior vena cava was either markedly narrowed or obliterated at the brim of the pelvis, the main circulation of opaque medium extending via the paraspinal veins and the ascending lumbar veins. A considerable reflux of opaque material into the greatly distended pelvic veins invariably occurred. A constant branch, the ascending lumbar vein, was one of the larger collateral branches and invariably arose from the left common iliac vein a few inches from the origin of the inferior vena cava. With too high a pressure, as when opaque material was injected by a pressure injector, passage along this vein occurred even in the absence of caval obstruction.

In cases where inferior vena cavography was performed after elective cesarean section and forward traction on the uterus, using two long catgut sutures to relieve pressure on the affected inferior vena cava, the cavogram showed a return to normal. The speed with which the roentgen appearances returned to normal suggests that the tributaries normally remain open and readily available. One may speculate what the effects of this raised pressure on the renal veins are and what part they play in upsets of renal function in pregnancy.—*Eugene J. McDonald, M.D.*

Scott, D. B. Inferior vena caval occlusion in late pregnancy. *Proc. Roy. Soc. Med.*, Aug., 1964, *57*, 705. (From: Royal Infirmary, Edinburgh, Scotland.)

That the supine position can cause acute hypotension in late pregnancy has been known for several years. In 3–5 per cent of patients, this hypotension is very marked, the systolic blood pressure falling to below 80 mm. Hg (sometimes as low as 50 mm. Hg), and rising to normal rapidly after the patient is turned onto her side. It seems that the venous return to the heart along the inferior vena cava (IVC) is being obstructed in these patients.

Most of the previous work on venous pressure in pregnancy had been done with simple water manometers which, unfortunately, cannot measure rapid changes and do not record continuously. Modern electronic methods using pressure transducers allow for continuous monitoring of venous pressure, rapid changes being easily detected.

When pressure recordings are made in late pregnancy (all cases were about to undergo cesarean section and none showed evidence of the hypotensive syndrome), quite a different picture is seen. The resting pressure in the supine position is very high (18–24 mm. Hg) and comparable with the level reached in nonpregnant cases when the IVC is occluded manually. If, during the operation, the uterus is lifted forwards off the IVC, a similar pressure drop is seen. When the baby and placenta are delivered, the pressure falls to the normal nonpregnant levels.

It was deduced from the pressure studies that a marked degree of occlusion of the inferior vena cava occurs in the supine position in late pregnancy.—*Eugene J. McDonald, M.D.*

Kerr, Melville G. Clinical implications of inferior vena caval occlusion in pregnancy. *Proc. Roy. Soc. Med.*, Aug., 1964, *57*, 705–706.

(From: Department of Obstetrics and Gynaecology, University of Edinburgh, Scotland.)

The author's observations on inferior vena caval (IVC) flow in pregnancy may be summarized as follows: When a patient in the third trimester of pregnancy lies in the supine position, the gravid uterus normally compresses the IVC from its formation by the union of the common iliac veins up to the level of the fundus of the uterus. Blood returning from the pelvis and lower limbs is redirected via alternative collateral channels. An appreciation of these observations may modify present interpretation of some important physiologic and pathologic features of pregnancy.

The postural effect is important in the assessment of cardiac output in pregnancy. The pattern of change in cardiac output throughout pregnancy remains a subject of controversy, but the generally accepted view is that there is a gradual increase of 20–30 per cent by the end of the second trimester, followed by a steady return towards prepregnancy levels by term. However, most, if not all, measurements of cardiac output in pregnancy have been made in the supine position, and consequently the mechanical factors which were described will operate. In these circumstances one may speculate that this late decremental phase of cardiac output may be partly a postural artifact, applicable only to the supine position.

Renal blood flow is said to increase rapidly in early pregnancy, then fall steadily to prepregnancy levels by term. This mechanical factor may be relevant to the postulated reduction in renal blood flow in late pregnancy.

Furthermore, renal function in late pregnancy is profoundly influenced by posture. The explanation of this postural effect is still obscure. Many factors could be implicated. There is a reduction in cardiac output and renal blood flow in the supine position, and furthermore the gravid uterus may directly compress the ureters and renal veins. Present studies show that the renal veins occupy a vulnerable position in that they drain into a segment of the IVC which is occluded in the supine position. While there are adequate collateral channels for blood returning from the pelvis and lower limb, there is no alternative venous drainage from the kidney.

Mengert suggested that IVC occlusion might be the cause of some cases of premature separation of the placenta. The explanation of Mengert's observations probably lies nearer the uterus. It is, in practice, difficult to occlude the IVC manually in the presence of the gravid uterus. The critical factor in this experiment was probably occlusion of the uterine veins rather than the IVC.—*Eugene J. McDonald, M.D.*

Skeletal System

PHELAN, JOHN T. Aneurysmal bone cyst. *Surg., Gynec. & Obst.*, Nov., 1964, *119*, 979–983. (From: Department of Surgery, Roswell Park Memorial Institute, New York State Department of Health, Buffalo, N.Y.)

Aneurysmal bone cysts were first described by Jaffe and Lichtenstein in 1942. Prior to this, a variety of names reflecting the possible origin of this lesion was used.

Five origins have been proposed. "A typical giant cell tumor" reflected the concept that an aneurysmal bone cyst represented a variant of a giant cell tumor; more recently these two entities have been separately described. Jaffe had previously suggested that an aneurysmal bone cyst was the consequence of hemorrhage into a pre-existing benign lesion which was then destroyed. Considered less likely is the possibility that this lesion represents a reparative process of a subperiosteal hematoma initiated by trauma. The pathologic features led Lichtenstein to postulate the widely accepted hypothesis that the cyst is an osseous response to an abnormal local hemodynamic factor such as an arteriovenous fistula or an acute venous occlusion.

Clinically, the lesion occurs most often in the 10 to 25 year age group. Three-fourths of all aneurysmal bone cysts involve the shaft of a long bone or the vertebral column, usually the neural arch or spinous process. The skull, hands and feet are rarely affected. Symptoms of pain and swelling are present unless the lesion is located near a joint or the vertebral column.

Roentgenographically, a fusiform, eccentrically placed, expansile lesion with a soap bubble appearance and located in the shaft of a long bone is quite characteristic of an aneurysmal bone cyst. A lesion confined to the cortex, a flat bone or a short bone is not distinctive in appearance.

Pathologically, the cyst, filled with unclotted blood, balloons out the cortex and erodes the medullary cavity. Microscopically, the cyst contains a fibrous connective tissue, honeycombed with blood filled spaces and collections of giant cells.

Curettage and packing with bone chips, if necessary, are advocated as the treatment of choice for this benign lesion. Irradiation is reserved primarily for cysts inaccessible to surgical treatment.—*John T. Underberg, M.D.*

SADLER, ARTHUR H., and ROSENHAIN, FELIX. Occurrence of two unicameral bone cysts in the same patient. *J. Bone & Joint Surg.*, Oct., 1964, *46A*, 1557–1560. (Address: Dr. Sadler, 105 Stevens Avenue, Mount Vernon, N.Y.)

The greatest growth of solitary bone cysts occurs during childhood and adolescence. Rarely are they seen before the age of 4 and seldom active after the age of 21. The commonest sites are at the metaphysial ends of the upper portions of the femur, humerus and tibia. Their appearance outside the long bones is unusual, although occasionally cysts are found in the calcaneus. Theories as to their origin vary from trauma to infection.

The authors report the case of a 10 year old Negro boy who was first seen in 1957 because of a pathologic fracture through a cyst in the left humerus. The patient was treated surgically over a period of several years for recurrence of the cyst. In September, 1961, a bone survey revealed a cystic lesion at the junction of the middle and distal thirds of the left tibia; on surgical exploration, it proved to be a unicameral bone cyst.

The authors state that to their knowledge a similar case of 2 unicameral bone cysts in one patient has not been previously reported.—*E. Arnoldi, M.D.*

DUNBAR, J. S., OWEN, H. F., NOGRADY, M. B., and MCLEESE, R. Obscure tibial fracture of infants—the toddler's fracture. *J. Canad. A. Radiologists*, Sept., 1964, *15*, 136–144 (From: Montreal Children's Hospital, Montreal, Quebec, Canada.)

The obscure, nondisplaced spiral fracture of the distal tibia most frequently seen in the age group from 9 months to 3 years is appropriately termed the "toddler's fracture" as it occurs when weight bearing is just beginning. This is frequently undiagnosed because of its obscurity and a lack of general awareness of it.

Clinically, the child usually presents with a history of failing to bear weight on the leg, and a history of trauma may be unknown or appear quite minimal. There may be no noticeable swelling of the extremity, but the child may exhibit increased irritability. Physical examination should begin with the unaffected extremity so as not to elicit premature crying and an apparent lack of localization of physical findings. Manipulation of the affected leg should also be preceded by gentle testing of the skin temperature on both sides, as there is frequently a detectable slight increase in heat over the lower anterior shin of the involved leg. Point tenderness and thus localization may be subsequently elicited by appropriate maneuvers leaving this area of examination until the last.

Roentgenologic study may demonstrate an obvious recent nondisplaced spiral oblique fracture of the distal shaft of the tibia, which frequently is seen in only 1 of the anteroposterior, lateral, or oblique projections. On occasion, no osseous abnormality is demonstrable until a few days to 2 weeks later, when repeat roentgenograms may reveal the fracture line and/or subperiosteal new bone formation or sclerosis about the fracture margins. Rarely, the only finding initially may be roentgenographic evidence of subcutaneous and deep muscular edema, the degree of which is not obvious clinically as swelling. The fibula characteristically remains intact.

The most common misdiagnoses are osteomyelitis and bone tumor. One case reported had the syndrome of unrecognized multiple skeletal trauma.

Treatment for cases diagnosed early consisted of immobilization in a plaster cast for a period of 3–4 weeks.—*Donald M. Monson, M.D.*

FIELDING, J. WILLIAM. Radio-ulnar crossed union following displacement of the proximal radial epiphysis: a case report. *J. Bone & Joint Surg.*, Sept., 1964, *46A*, 1277–1278. (Address: 105 East 65th Street, New York 21, N.Y.)

The author reports this case because of its rarity.

The patient was an 11 year old boy who injured his elbow from a fall. Roentgenograms showed a fracture through the proximal epiphysis of the radius with some impaction and displacement. There was moderate angulation. The displacement was not corrected on a single attempt at reduction. Splints were applied to produce pressure over the radial head and the patient was started on exercises 3 weeks later.

Examination 1 year later showed loss of pronation and supination and the roentgenograms revealed a crossed bony union between the radius and ulna. There was still deformity of the head present.—*George L. Sackett, Jr., M.D.*

ABELL, JOE M., JR., and HAYES, JOHN T. Charcot knee due to congenital insensitivity to pain. *J. Bone & Joint Surg.*, Sept., 1964, *46A*, 1287–1291. (Address: Dr. Abell, Jr., 1506 Guadalupe Street, Austin, Tex.)

Congenital insensitivity to pain is a rather rare condition.

The authors discuss this disorder briefly and report a case of a 17 year old boy who developed a neurotrophic arthropathy of the left knee, resulting in considerable deformity and disability which had been unsuccessfully treated previously.

Following an arthrodesis of the knee joint the patient was able to get around much better.—*George L. Sackett, Jr., M.D.*

MAJID, M. A., MATHIAS, P. F., SETH, H. N., and THIRUMALACHAR, M. J. Primary mycetoma of the patella. *J. Bone & Joint Surg.*, Sept., 1964, *46A*, 1283–1286. (Address: L. Col. M. A. Majid, Armed Forces Medical College, Poona, India.)

Mycetoma is a chronic granuloma caused by the invasion of skin or underlying tissues by a variety of fungi; it rarely affects the bone.

The authors report a case of mycetoma of the patella which was previously unreported as a site of involvement.

The patient was a 13 year old boy who developed pain in the region of the patella about 6 weeks after a fall. Swelling developed gradually over the next 4 months.

Roentgenograms showed a large cystic area involving the lateral half of the patella with new bone formation seen anteriorly. The lesion was fairly well circumscribed.

The area was explored and the prepatellar bursa was found to contain dirty gray fluid with a few black granules. There was a tract connecting the bursa with a large cavity in the patella extending into the tissues posterior to the ligamentum patellae. The patella, prepatellar bursa and infrapatellar fat pad were removed, the impression being that the lesion represented a mycetoma. Mycologic study showed that the organism was *Madurella mycetomi*.—*George L. Sackett, Jr., M.D.*

Horner, David B. Lumbar back pain arising from stress fractures of the lower ribs: report of four cases. *J Bone & Joint Surg.*, Oct., 1964, *46A*, 1553–1556. (Address: 233 North Prairie Avenue, Inglewood, Calif.)

Adding to the known causes of low back pain, the author reports 4 patients with low back pain secondary to fracture of the lower ribs. The presenting symptoms of this group were pain in the low back with associated discomfort and difficulty in breathing. Tenderness to palpation in the area of the ribs led to the suspicion of rib fracture. The diagnosis subsequently was confirmed by roentgenograms.

In no case was there a history of a direct blow to the involved area nor was there an episode of violent coughing or sneezing. However, a common finding proved to be the history of previous violent muscle exertion.

The mechanism of the stress fractures is explained by the fact that below the level of the tenth rib, the external oblique muscle interdigitates with the latissimus dorsi, while above this level it interdigitates with the serratus anterior. This anatomic difference may account for the reason why floating ribs are less often involved in cough fractures but may be fractured during strenuous exertion.—*E. Arnoldi, M.D.*

Kirgis, Homer D. Problems in the management of the "compensation" patient with the lumbar disk syndrome. *South. M. J.*, Oct., 1964, *57*, 1152–1156. (From: Section on Neurosurgery, Ochsner Clinic, New Orleans, La.)

This article deals with the ever-present problem of patients with low back injury and compensation for loss of time resulting therefrom. A study was made of 100 patients with such injury who were denied proper treatment and compensation because their cases were handled at the beginning by company or insurance company physicians.

The subject of important medical testimony is discussed; the author believes that such impartial medical judgement should be available at the onset of the problem rather than after the case reaches the trial judge.

The opinion is advanced that the injured employee should be cared for by his family physician rather than by a company physician because the company physician is an employee of the insurance carrier is primarily interested in reducing compensation claims.

One typical case history is given.—*J. H. Harris, M.D.*

Brown, Michael, and Battle, John D., Jr. The effect of urography on renal function in patients with multiple myeloma. *Canad. M. A. J.*, Oct. 10, 1964, *91*, 786–790. (From: Department of Hematology, The Cleveland Clinic Foundation, Cleveland, Ohio.)

Since 1954, it has been well known that intravenous urography performed on patients with multiple myeloma carries a definite risk of producing renal failure. The probable mechanism, according to experimental and pathologic evidence, is one of intratubular precipitation of protein and severe tubular obstruction.

Of 227 patients with multiple myeloma between 1940 and 1959, 39 had intravenous urography. In 4, there was clinical or laboratory evidence of deterioration in renal function soon after intravenous or retrograde urography, followed by death. In these 4 patients, the blood urea nitrogen level was elevated in 3, and probably the fourth as well, prior to the procedure. Two of the patients showed no adverse effects from one or more intravenous studies, but severe renal failure developed after retrograde pyelography; apparently these are the first reported cases of acute renal failure following retrograde pyelography in the presence of multiple myeloma. In the 35 patients in whom no complications developed, blood urea levels were less than 40 mg. per cent in 17, elevated in 8, and not determined in 10.

Although little detailed information is available concerning the effect on the normal kidney of intravenous contrast media in the concentrations used in urography, the risk of producing acute oliguria in patients without multiple myeloma is negligible. Unless we know the "spontaneous" oliguria and uremia rate in patients with multiple myeloma, it is difficult to assess the risk of urography. The precipitation of azotemia or aggravation of pre-existing azotemia after intravenous or retrograde urography appears to indicate a causal rather than a coincidental relationship. The precipitation of protein in the tubular lumen with tubular dilatation is the most common lesion found at autopsy, and appears to be the most likely major cause of renal insufficiency. The factors responsible for such aggravation are not clear, but dehydration both from water restriction and from purgation probably is of importance.—*Mark D. Reiss, M.D.*

Bywaters, E. G. L. Brief notes on the natural history of rheumatoid arthritis. *Canad. M.A.J.*, Sept. 12, 1964, *91*, 606–608. (From: Medical Research Council Rheumatism Research Unit, Taplow, Maidenhead, Berks, England.)

The author has made a long-term study of 250 consecutive unselected patients with rheumatoid arthritis between 1939 and 1963. He states that improvement occurs in the majority of patients in the first 5 years of the disease and is maintained over the next 5 years. Most hospital studies are biased by selection, in that 80 per cent of rheumatoid patients were never referred to the hospital and those with mild disease often failed to consult their doctors at all. Half of the patients in this series have died, on the average, slightly earlier than they would have done without rheumatoid arthritis, usually of "fairly ordinary diseases." A few deaths were specifically due to rheumatoid arthritis. The incidence of infection as a cause of death was suspiciously higher.

The author reports that certain patients develop a peculiar small brown nodule in the pressure areas of the fingers. These are related to small trauma and disappear with rest of the hands. These changes he relates to an obliterative endarteritis associated with the subcutaneous nodules of rheumatoid arthritis in a very high proportion of cases and also with a positive Rose-Waaler test for rheumatoid factor. Rheumatoid joint changes are, however, more apt to be associated with activity of the joint as indicated by a single patient reported by author who had hemiplegia with multiple joints affected on the nonhemiplegic side of his body and none on the paralyzed side. In this patient obliterative vascular lesions were demonstrated by arteriography bilaterally.

The author states that the presence of rheumatoid factor determines the vascular changes and perhaps some of the other complications, but this is not apparently related to the joint involvement which is essentially a localized disease.—*Donald S. Linton, Jr., M.D.*

Brannan, Harold M., Good, C. Allen, Divertie, Matthew B., and Baggenstoss, Archie H. Pulmonary disease associated with rheumatoid arthritis. *J.A.M.A.*, Sept. 21, 1964, *189*, 914–918. (Address: Mayo Clinic, Rochester, Minn.)

Clinical records of patients in whom a diagnosis of rheumatoid arthritis was made at the Mayo Clinic in a 10 year period, 1950 through 1959, were reviewed. The group comprised 27 patients having extensive pulmonary disease and definite rheumatoid arthritis. Eighteen of these were men and 9 were women. The average age was 57 with the oldest patient being 75 and the youngest 33. Pulmonary involvement preceded arthritis in 3 instances and arthritis preceded pulmonary disease in 19 cases. Sixteen of the patients had pulmonary involvement within 2 years of the time of the onset of their arthritis, and in 5 patients the onset of the disease in the two systems was simultaneous. Repeated simultaneous exacerbations of disease in both joints and the lungs were present in 12 patients.

Roentgenograms of the patients with a recent onset of pulmonary disease showed soft, fluffy, patches of involvement. The process usually had a "cotton-like" appearance. The early processes were seen more often in the bases, but occasionally the upper lobes were involved. Serial roentgenograms were available for 3 patients showing the progressive changes from soft basilar infiltrates to extensive diffuse fibrosis. Areas of initial involvement were seen to clear, although clearing was always incomplete and some degree of residual fibrosis was uniformly present. With exacerbations of the pulmonary disease, new areas of soft infiltrate would become superimposed on the older fibrosis until the lungs were completely involved. Honeycombing was not encountered. Pleural effusion or pleural thickening was suggested in 6 of the patients. Cases of pleural effusion without obvious parenchymal involvement were not included in the study.

Biopsy of lung tissue in 5 of the 27 cases showed proliferation of interstitial fibrous tissue, both peribronchial and within the alveolar walls. Lymphocytes and plasma cells had infiltrated the interstitial regions. Occasionally, the infiltrating cells were aggregated in definite foci. Thickening of the smaller blood vessels was present in each case. There were no nodules.

The question of whether bilateral interstitial pneumonitis and subsequent fibrosis of the lungs may be a manifestation of rheumatoid arthritis is still disputable. Except in those cases in which rheumatoid granulomas are found in the lungs, the histopathology in the lungs is not specific. In those cases in which rheumatoid nodules have been found in the parenchyma of the lung, interstitial pneumonitis or fibrosis was present in all cases.

In this series the higher incidence of the pulmonary disease in men is noteworthy. Seven roentgenographic reproductions illustrate the progressive changes found.—*Donald S. Linton, Jr., M.D.*

Robillard, Rosario, Gagnon, Paul-A., and Alarie, Roger. Diabetic neuroarthropathy: report of four cases. *Canad. M. A. J.*, Oct. 10, 1964, *91*, 795–804. (From: Diabetic, Nutritional, and Orthopedic Services, Hôpital du Sacré-Coeur, Montreal, Quebec, Canada.)

Case reports of 4 patients with long standing diabetes mellitus and neuroarthropathy involving the feet are presented. The foot was found to be the area involved in 91 of 100 cases reviewed in the world literature. The clinical picture is usually that of long-standing and poorly controlled diabetes. Progressive loss of shape in the involved foot, with eventual "rocker-bottom" appearance, and chronic plantar ulcerations occur. The common denominator in these cases is the total absence of pain when walking on this deformed foot. Varying degrees of peripheral neuropathy occur, with loss of position or vibration sense, and diminished deep tendon reflexes.

The roentgenographic findings resemble closely those in any Charcot's arthropathy: there are areas of bone lysis with fragmentation, joint-space obliteration and, later, marked destruction of the osteoarticular structure. The picture of metatarsal tapering or "sucked candy-stick" osteolysis is very common. At times, one can see an apparent bursting of the first metatarsal head.

The etiology has not yet been defined. Chronic infection, vascular ischemia, autonomic nervous system pathology have all been discarded as causative because of contradictory factors. Trauma, whether repeated "micro-trauma" or a single event, due to the absence of pain, plays a large part in the development of the clinical picture.

The differential diagnosis includes: lues, syringomyelia, alcoholism, osteomyelitis, and excessive steroid intake. Medical treatment with multiple vitamins has been recommended. The most successful orthopedic treatment has been the use of a walking cast.—*Mark D. Reiss, M.D.*

Hunt, David D. Problems in diagnosing osteoarticular tuberculosis. *J.A.M.A.*, Oct. 12, 1964, *190*, 95–98. (From: Division of Orthopedic Surgery, Stanford University School of Medicine, Palo Alto, Calif.)

When tuberculosis of bone presents in other than the classic sites of the spinal column and about the sacroiliac, knee and hip joints, diagnosis is frequently delayed, particularly when there are no signs of pulmonary involvement. Reported here are 5 of 10 cases seen by the author in the past year which had either atypical features or appearances in their tarsal, hip, proximal humerus, and sternoclavicular joint locations, without evidence of pulmonary lesions.

Clinically, they all had palpable masses and 2 of them had draining sinuses, with varying degrees of redness and pain about the area. All those on whom laboratory tests were performed had normal white blood cell counts and differentials, elevated sedimentation rates and positive tuberculin reaction. Smears and cultures of available drainage material were negative for acid-fast bacilli and revealed only *Staphylococcus aureus* or *Streptococcus* organisms.

Roentgenographically, there was localized bone destruction with occasional sequestrum formation and limited degrees of localized bone sclerosis. Not all cases had regional bone atrophy, but there was relative preservation of the cartilage spaces of the joints. The initial diagnostic impressions were almost uniformly those of other diseases such as neuropathic changes, neoplasms, or pyogenic osteomyelitis.

The diagnosis was made in each case by biopsy of the affected bone, with histologic examination revealing granuloma formation typical of tuberculosis, which was confirmed by subsequent growth of acid-fast bacilli on culture of this material. Following a presumptive diagnosis by histologic examination, therapy was immediately started with various combinations of streptomycin, isoniazid, and aminosalicylic acid. Extensive debridement was performed in 4 cases and a below knee amputation was done in one. Four of the patients appear to have responded well to treatment, with a fifth dying from a cerebrovascular accident 5 weeks after debridement of the tarsus.

Other extenuating circumstances for the frequent delay in the diagnosis of osteoarticular tuberculosis appear to be the decreasing incidence of this disease, along with its seemingly changing character, as it is now seen in more unusual locations and in older patients. Except for one patient in this report who was 13 years old, the age span was from 41 to 81 years. Prompt biopsy and tissue examination is extremely useful in establishing a presumptive diagnosis on the basis of which treatment can be instituted.—*Donald M. Monson, M.D.*

BLOOD AND LYMPH SYSTEM

Milne, Eric N. C. Selective and total cerebral angiography and arteriography of the great vessels in the root of the neck via percutaneous femoral puncture. *J. Canad. A. Radiologists*, Sept., 1964, *15*, 118–125. (From: McKeller General Hospital, Fort Williams, Ontario, Canada.)

Numerous approaches have been suggested for opacification of the vertebral and carotid systems with visualization of both the intracranial and extracranial portions. The author feels that in his experience, the catheter technique of percutaneous femoral puncture and selective cerebral angiography is much superior to direct puncture, or catheterization via brachial artery, subclavian artery or axillary artery approaches.

The technique depends upon the use of a preshaped flexible radiopaque intravascular Ödman catheter. This is passed, using the Seldinger method, to the ascending aorta. Injections are made: (1) while in the ascending aorta, (2) after the selective catheterization of the innominate artery, and (3) in the aorta near the takeoff of the left carotid and left subclavian arteries. These three injections with the use of properly applied blood pressure cuffs will adequately visualize the desired arterial circulation. The total amount of contrast material used for visualization of both carotids and both vertebrals should not exceed 120 ml., and much of this passes down the aorta.

Since atheromatous changes often occur at the mouths of the great vessels and manipulation of a catheter during selective placement could dislodge a plaque into the carotids or vertebrals, a preliminary injection is made in the aorta. If changes are present, selective catheterization is not done. In such cases, angiograms are made by injection into the aorta with alternate compression of the carotids and occlusion of the axillary artery by blood pressure cuffs.

In a series of 110 cases, this technique was felt to be preferable to the previously mentioned alternatives because it requires only one puncture, is simple to perform, has a low rate of complications and allows visualization of the entire course of the carotid and vertebral arteries.—*Alan G. Greene, M.D*

Thompson, L. K., III, and Anlyan, W. G. An angiographic evaluation of swollen limbs. *Surg., Gynec. & Obst.*, Oct., 1964, *119*, 743–748. (From: Department of Surgery, Duke University Medical Center, Durham, N. C.)

Arteriography, phlebography, and lymphangiography were used in the evaluation of swollen limbs in 96 patients.

Swollen limbs are usually due to: (1) congenital or idiopathic lymphedema; (2) obstructive lymphedema secondary to neoplasm, irradiation, trauma, or surgery; (3) postphlebitic venous insufficiency; or (4) angiomatous malformation.

In studying the peripheral lymphatic system, an initial subcutaneous injection of sky blue, diluted in a 1:1 ratio with 1 per cent xylocaine, was employed. Incision was made proximally, permitting identification of a lymphatic channel as well as a suitable venous channel for further injection. In idiopathic or congenital lymphedema, the blue dye spread through the lymphatics over the dorsum of the foot readily, but this did not occur in the obstructive lymphedema cases. Attempts to cannulate the lymph channels may be difficult in congenital lymphedema because they are hypoplastic. Venograms in these cases usually show normal vessels, making differential diagnosis easy. In metastatic disease, combining lymphangiograms with venograms and arteriograms may give a complete picture of the deformity causing the swollen limb.

Chlorophyll injected with ethiodol has been helpful in lymphangiography since it stains the lymph nodes making it possible for the surgeon to identify them at operation.

Use of all three methods of study has shown that congenital anomalies may involve all vascular and lymphatic systems concomitantly.—*Richard E. Kinzer, M.D.*

Sage, Harold H., Sinha, Birendra K., Kizilay, Dogan, and Toulon, Rudolph. Radioactive colloidal gold measurements of lymph flow and functional patterns of lymphatics and lymph nodes in the extremities. *J. Nuclear Med.*, Aug., 1964, *5*, 626–642. (From: Department of Surgery, New York University School of Medicine and The Guggenheim Institute of Dental Research, New York University College of Dentistry, New York, N. Y.)

The authors have devised a radioisotope technique for using colloidal gold (Au^{198}) for the combined and simultaneous study of the dynamics and functional pathways of lymph flow as well as lymph node pick-up and filtration function. An extensive comparison between I^{131} human serum albumin and colloidal gold has been made in search for an ideal isotopic material for studying the lymph flow. They present conclusive evidence that the radiogold is far superior for this determination.

The initial studies in the lower extremity were made by the injection of a 0.1 cc. volume of colloidal Au^{198} into the subcutaneous tissues of the dorsum of the foot. Radioactivity measurements were made by external counting, utilizing a 3 inch sodium iodide crystal and extensive collimation. Almost 100 per cent of the colloidal gold can be accounted for by external volume counting and traced throughout the lymphatic system.

The lymph flow is measured: (1) by the disappearance rate from the site of injection, reflecting both the inflow amount of lymph and the state of competency of the lymphatics; (2) by measurements of segments, indicating the distribution of the material in the lymphatic system through arbitrarily designated anatomic segments; (3) by the rate and quantity of pick-up in the lymph nodes, separate measurements being made of the superficial femoro-inguinal and the deep ilio-aortic lymph nodes; (4) by the rate and quantity of deposition in the liver and spleen, representing complete by-pass of the lymph nodes and entrance into the thoracic duct and blood stream.

The isotope technique is well documented and the authors devised a water phantom to reproduce the geometry of the various counting segments. This provided correction factors to be added to the *in vivo* measurements made by external counting. Scintiscanning of the femoro-inguinal lymph nodes was performed routinely. The disappearance rate was recorded as per cent of injected amount of colloidal gold, while all other measurements were recorded as a per cent of the amount of colloidal gold which had disappeared from the site of injection.

Disappearance rates in normal humans following subcutaneous injection of the lower extremity ranged from 18 to 39 per cent at 24 hours. They also measured the disappearance rate by intramuscular and intradermal injections. The tracer material was followed from the point of injection through the progressive anatomic segments until deposition in the lymph nodes. The amount of isotope by-passing the lymph nodes and becoming deposited in the liver was also measured.

It was demonstrated that from 80 to 100 per cent of the colloidal gold which disappears from the site of injection is picked up by the lymph nodes within 6 to 12 hours. The effect of exercise is to increase the progression of the tracer material. It was also found that if the colloidal gold enters a lymph node, it remains there for at least 1 week, the duration of the study.

The authors have applied their technique and measurements to a large group of patients with abnormal extremities. These are to be reported in detail in a future publication.—*Millard N. Croll M.D.*

Jing, Bao-Shan, McGraw, John P., and Rutledge, Felix N. Gynecologic applications of lymphangiography. *Surg., Gynec. & Obst.*, Oct., 1964, *119*, 763–772. (From: Section of Diagnostic Radiology, Department of Radiology, and the Section of Gynecology, Department of Surgery, The University of Texas M. D. Anderson Hospital and Tumor Institute, Houston, Tex.)

Specific clinical applications of lymphangiography in diagnosing malignant disease of the female genital organs are presented with case examples and a brief discussion of each. In order of usefulness they include: (1) detection of lymph node metastases in new cases; (2) aid in selection and evaluation of surgical procedures; (3) help in the decisions regarding methods and evaluation of irradiation; (4) determination of lymph node involvement in local recurrence; (5) evaluation of advisability of, and response to, chemotherapy; (6) consideration of lymph node metastases as a contributing cause of urologic complications; and (7) demonstration of post-lymphadenectomy complications.

Direct demonstration of lymph node metastases from carcinoma of the female genitalia can only be obtained by lymphangiography. The limitations of the technique are pointed out. The hypogastric, superior superficial inguinal, and obturator lymph nodes cannot be visualized. Lymph nodes with small metastatic lesions and those with 'complete replacement by malignancy are recognized only with difficulty. Nonmalignant changes in the lymph nodes, together with anatomic variations, may serve to confuse the issue.

The authors report that no serious complications have occurred in their series of 421 patients; 155 of these had gynecologic malignancies. Less serious reactions have been lymphangitis, wound infection and febrile reactions. The contributing factors to embolic phenomena in the pulmonary vascular tree are briefly discussed.—*N. K. Richardson, M.D.*

GENERAL

Carter, A. E., and Eban, R. A case of bilateral developmental abnormality of the popliteal arteries and gastrocnemius muscles. *Brit. J. Surg.*, July, 1964, *51*, 518–522. (From: The King Edward Memorial Hospital, Ealing, London, England.)

The gastrocnemius muscle phylogenetically develops in man so that the tibial-sided head is larger and extends farther up the shaft of the femur than the smaller and more poorly developed fibular sided head.

The authors present a case of a 16 year old male in which this usual situation is reversed. The case illustrates a developmental failure on both sides of full migration of the tibial-sided head of the gastrocnemius muscle with reduction of these heads to a muscular (right) and fibrous (left) band. The popliteal artery, which normally passes between the gastrocnemial heads, in this particular case ran medial to the tibial band. As a result of the intermittent pressure on the popliteal artery by the band, subsequent narrowing of the artery developed with associated post-stenotic dilatation and plaque formation on the right side.

Eventually, a complete occlusion of the right popliteal artery occurred which necessitated clot removal and saphenous vein patch grafting. Surgical release of both bands was performed with insertion and stitching of the bands alongside the normal head of the gastrocnemius muscle. Upon release, the popliteal arteries pulsated and appeared normal.

Femoral arteriograms, together with sketches of the developmental abnormalities are presented.—*Donald S. Faust, M.D.*

Bean, William J., and Nice, Charles M., Jr. Experiences with mammography in a teaching hospital. *South. M. J.*, Oct., 1964, *57*, 1168–1171. (From: Department of Radiology, Tulane University School of Medicine, and Division of Diagnostic Radiology, Charity Hospital, New Orleans, La.)

The authors have attempted to determine the value of mammography under conditions that would be similar to an average radiologic practice. The low kv. roentgenographic technique of Egan was followed insofar as the 200 ma. Picker machine and roentgen ray tube would permit. Student technicians made the roentgenographic examinations and the studies were interpreted by residents in Radiology at the Charity Hospital, New Orleans.

This study was carried out over a 2 year period, during which time over 400 breasts were examined. Biopsy was performed on 150 breast lesions.

The accuracy of all the roentgenographic examinations, made under the varied abilities of the resident radiologists, was better than 90 per cent for both benign and malignant conditions.—*John H. Harris, Jr., M. D.*

RADIOISOTOPES

HIGGINS, H. PATRICK, ELKAN, IVAN, DIOSY, ANDREW, BAYLEY, T. ARNOLD, and BUCKLEY, GLORIA C. Prognostic value of high 10-minute I^{131} uptake in non-toxic goitres. *Canad. M. A. J.*, Sept. 26, 1964, *91*, 689–693. (From: St. Michael's Hospital, Toronto, Ontario, Canada.)

The 10 minute I^{131} uptake may indicate which non-toxic goiter patients would respond to T3 therapy.

A selected group of 42 patients with nontoxic goiters and elevated 10 minute I^{131} uptakes was treated with L-triiodothyronine (100 μg. per day up to 36 months). Response in terms of reduction in gland size was noted in all cases. Ten patients showed marked regression as early as 1 week.

Prior to treatment, 20 of the 42 patients were examined for antithyroid antibodies by standard methods. Virtually all of these titers were very low or negative. Supported by clinical impressions, Hashimoto's disease was thought to be unlikely in each case. Since surgical exploration was not done, the exclusion of carcinoma or lymphadenoid goiters must rest on the clinical and biochemical profile, including scanning.

A brief discussion of the possible etiology of this condition is given with attention called to the possibility of inborn errors of thyroxine metabolism. Perchlorate wash-out trials were done in 5 cases and were negative.

The combination of mild hypothyroidism found in most of these patients and the advisability of preventing chronic TSH stimulation of the thyroid gland makes a trial of T3 therapy on these high uptake nontoxic goiter patients attractive.—*N. K. Richardson, M.D.*

SAITO, HIROSHI, SARGENT, THORNTON, III, PARKER, HOWARD G., and LAWRENCE, JOHN H. Whole-body iron loss in normal man measured with a gamma spectrometer. *J. Nuclear Med.*, Aug., 1964, *5* 571–580. (From: Donner Laboratory of Biophysics and Medical Physics, University of California, Berkeley, Calif.)

Many workers have measured the daily loss of body iron in man by studying the radioactivity in the blood, stool, urine, sweat and bile following the intravenous injection of radioiron. The authors felt that this parameter could be measured quite simply with the whole-body counter. A number of problems, however, complicated analysis of the data. Twelve normal male human subjects were used. A whole-body counter with a 9×4 inch crystal and a 100 channel pulse height analyzer was available with "1-meter-arc" geometry. Iron 59 citrate was administered intravenously. Ten subjects received a dose of 5 μc and 2 subjects received 18 μc, the latter doses having been incubated with plasma.

Immediately following injection, the radioiron appears in the plasma, but 24 hours later, the plasma level is less than 3 per cent of the administered dose. At this time, most of the radioiron has been taken up by red cell precursors in the bone marrow.

The authors measured the changes of whole-body radioactivity in all subjects for over 300 days. It was found that one day following injection, the whole-body count had decreased to 90 per cent of the initial value, but that it rose slowly and returned to an average of 97 per cent after 10 days, staying at this level without any perceptible change until 50 days. The initial loss of radioiron does not account for the 3 per cent decrease as based on measurement of activity found in stool and urine during this time. Analysis of the entire curve shows a predicted stepwise decrease in total body activity occurring approximately every 120 days.

The authors postulate that the changes in total and whole-body activity are due partly to loss from the body of the radioiron and partly to the changes in localization of the iron within the body. Death of the labeled population of red cells causes movement of radioiron to miscible tissue iron. Although the radioiron is then incorporated into new cells, some fraction remains in tissue. The authors calculated the body loss of radioiron as demonstrated in the whole-body activity curve to be 0.030 per cent per day. Analysis of the Fe^{59} loss in stool and urine was performed on only 2 of the subjects, those receiving the higher dosage of injected isotope. The total excreted activity curve shows 2 components: the rapid loss for a period of 8 to 10 days and then a slower loss thereafter. It is postulated that the initial rapid loss coincides with a period of exfoliation of the gastrointestinal epithelia. Urine loss must be attributed to exfoliation of the urogenital epithelia.

The excretion studies confirmed the whole-body activity curve representing an average normal iron loss rate of 0.030 per cent per day or 0.89 mg. per day. These figures are in reasonable agreement with the daily amount of iron absorption and of the work of other authors.

It is concluded that the whole-body counter is the simplest, most accurate method of measuring the loss of body iron.—*Millard N. Croll, M.D.*

Fava, G., and Roncoroni, L. Controlli autoptici sulla distribuzione nei vari organi del lipiodol radioattivo introdotto per via linfatica. (Autoptic controls of the distribution in various organs of the radioactive lipiodol introduced through the lymphatic channels.) *Radiol. med.*, July, 1964, *50*, 653–659. (From: Istituto di Radiologia dell'Università di Milano, Italy.)

In a previous communication the authors presented dosimetric data obtained by a scintillation counter located over the lymphatic trunks and abdominal organs of patients in whom radioactive lipiodol had been introduced by the usual method.

These data were also compared with dosimetric values obtained directly from abdominal lymph nodes removed at surgery, following a Wertheim hysterectomy.

The authors now present dosimetric data which were obtained by calculating the total radioactivity of the liver, spleen, thyroid, kidneys, brain, and lungs in specimens, following autopsy, and which were compared with the values obtained over the same organs, while the patients were still under treatment.

The results confirm the elevated radioactivity of the lymph nodes and rather poor uptake by the other organs. Furthermore, the dosimetric values obtained *in vivo* do not differ greatly from those noted in the specimens.—*A. F. Govoni, M.D.*

Rubin, Philip, and Levitt, Seymour H. The response of disseminated reticulum cell sarcoma to the intravenous injection of colloidal radioactive gold. *J. Nuclear Med.*, Aug., 1964, *5*, 581–594. (Address: Dr. Rubin, Chief, Division of Radiation Therapy and Radioisotopes, Strong Memorial Hospital, University of Rochester Medical Center, Rochester, N. Y.)

The use of systemically administered radioactive isotopes in the treatment of diseases of the lymphoid system has been attempted since the late 1930's. The first agent to be utilized was radioactive phosphorus 32 but this was abandoned because of the limited response both symptomatically and objectively. Since then, various radioactive colloidal compounds have been employed, the most frequent of which has been radioactive colloidal gold 198. The rationale for its use was the distribution of the administered material within the lymphoid macrophage system giving desired selective radiation effects in the diseases of this system. Sixty to 90 per cent of the intravenously injected radiogold is firmly retained in the liver and the remainder is about equally distributed in the spleen and bone marrow in the reticulo-endothelial cells.

The authors report 2 cases of diffuse reticulum cell sarcoma, where intravenously administered radioactive colloidal gold has been used in treatment. Of the 2 patients with disseminated disease treated in this manner, 1 has survived over 5 years.

The explanation for the successful outcome in the reported case of disseminated reticulum cell sarcoma is probably the fortuitous distribution of the disease paralleling the distribution of the radioactive colloidal gold. The authors do not believe that the good response is due to a spontaneous remission or to specific phagocytic activity in the reticulum sarcoma cells. For the agent to be effective therapeutically, the neoplastic process must be radiosensitive, microscopic in deposits as well as diffuse and homogeneous.

The authors suggest that intravenously administered radioactive colloidal gold may be a useful agent in lymphosarcomas with minute diffuse neoplastic involvement of the liver and spleen and possible minimal bone marrow involvement. It is of no value in the treatment of involved lymph nodes or large masses. Its major side effect is the production of bone marrow depression and thrombocytopenia. They suggest a dosage of no more than 50 mc intravenously.—*Luther W. Brady, M.D.*

Karp, Henry C., Garland, B. I., and Bruin, Nicco. Rehabilitation of a radioactive building. *Pub. Health Rep.*, Sept., 1964, *79*, 829–835. (Address: Mr. Karp, Radiological Health Section, Georgia Department of Public Health, Atlanta, Ga.)

The procedures that were employed in radioactive decontamination of a four-story building, utilized previously as a cancer clinic, are outlined.

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After a monitor survey, marking all areas of concentrated activity for vacuuming, scrubbing and mopping operations by protected personnel, the debris and all remaining removable fixtures in the building were transported and buried in steel drums under 10 feet of earth. Trisodium phosphate and hydrochloric acid followed by neutralization served as cleansers. Air sampling during acid use showed very low radioactive values.

During various steps of the survey and follow up cleaning procedures, radon seeds were discovered incorporated into some of the 9 layers of paint on the walls. Possible loss of needles into paint during redecoration was assumed.

The final measures in rehabilitation included a sealing process after re-monitoring revealed acceptable low level areas of radioactivity. However, since there was a high probability of future peeling and flaking of the multilayered paint, false ceilings and walls were installed in a way as to retain an access to the baseboard level for periodic safe removal of flaked debris.—*N. K. Richardson, M.D.*

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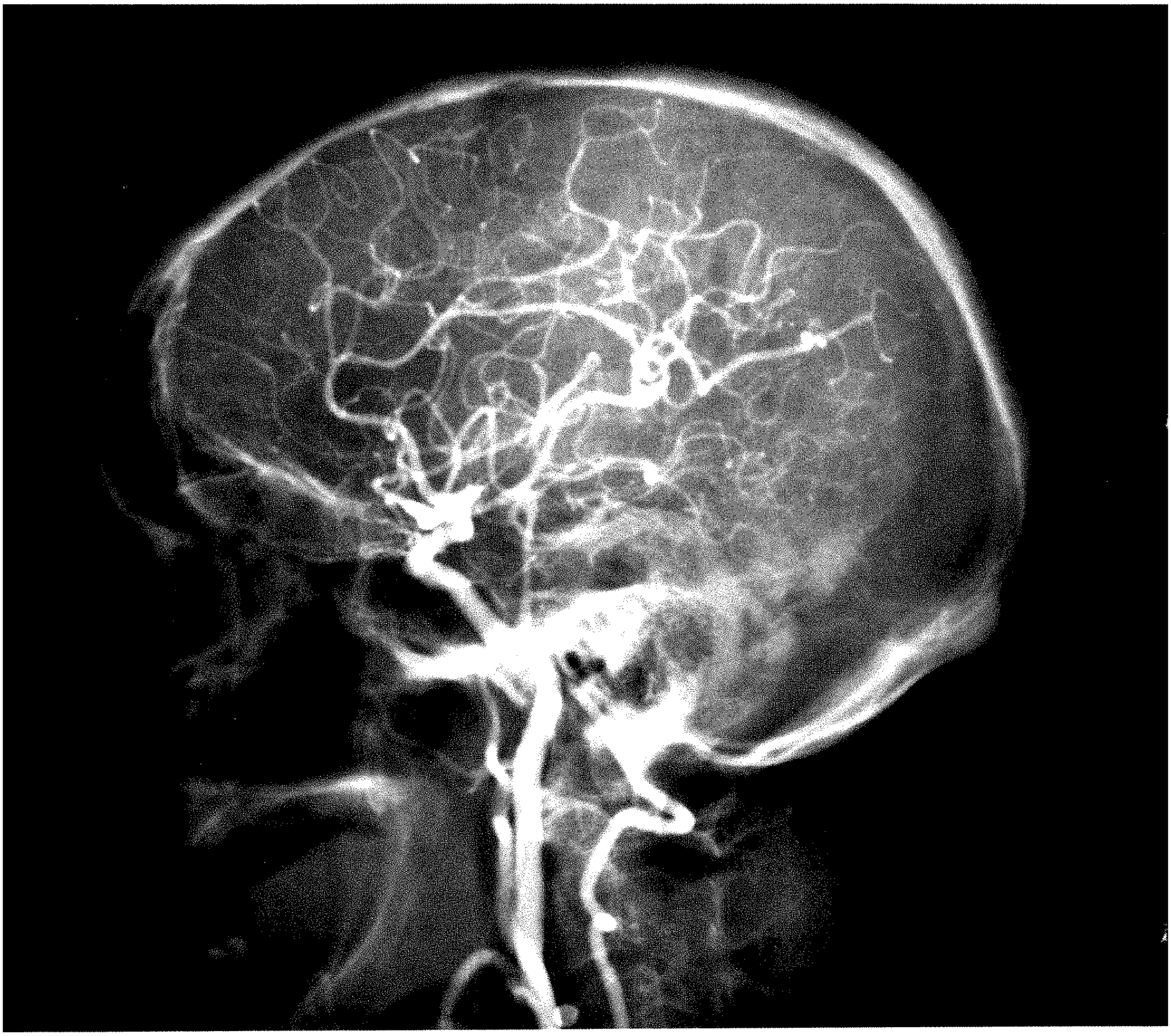

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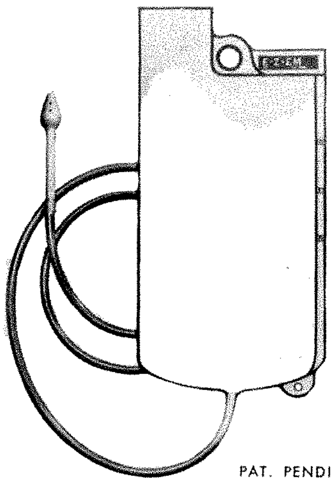

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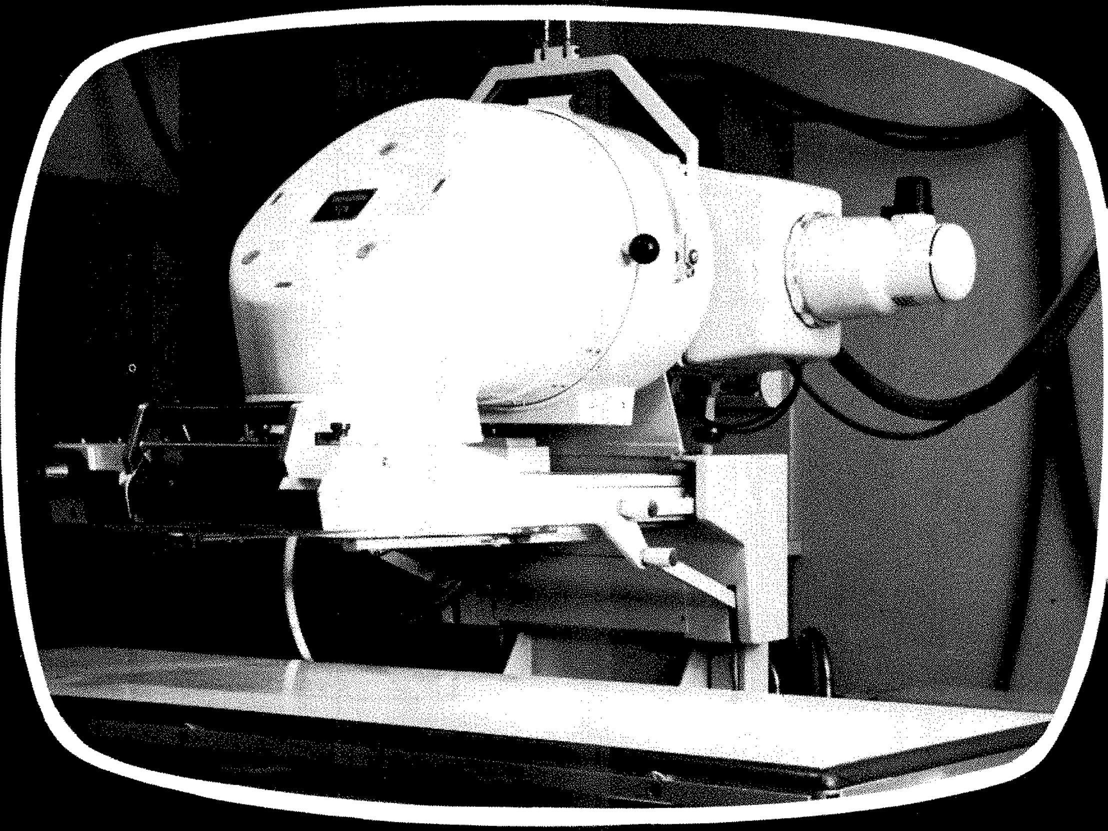

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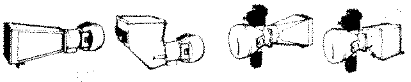

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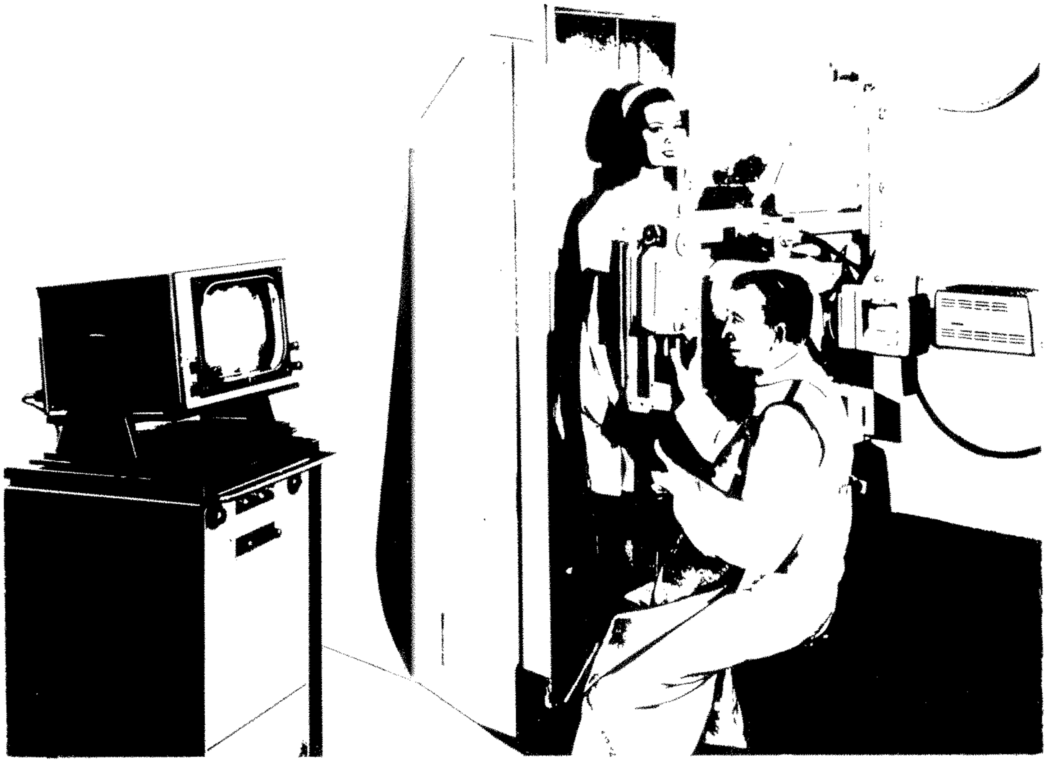

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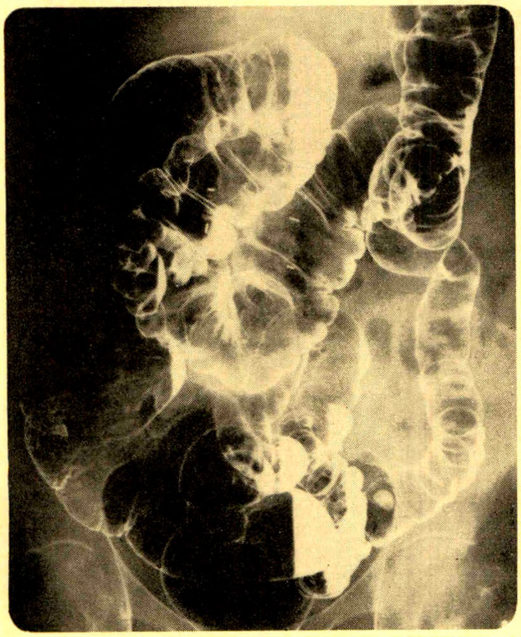

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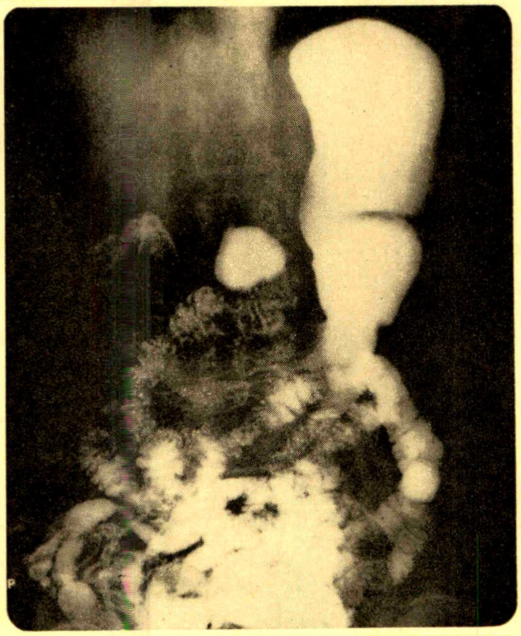

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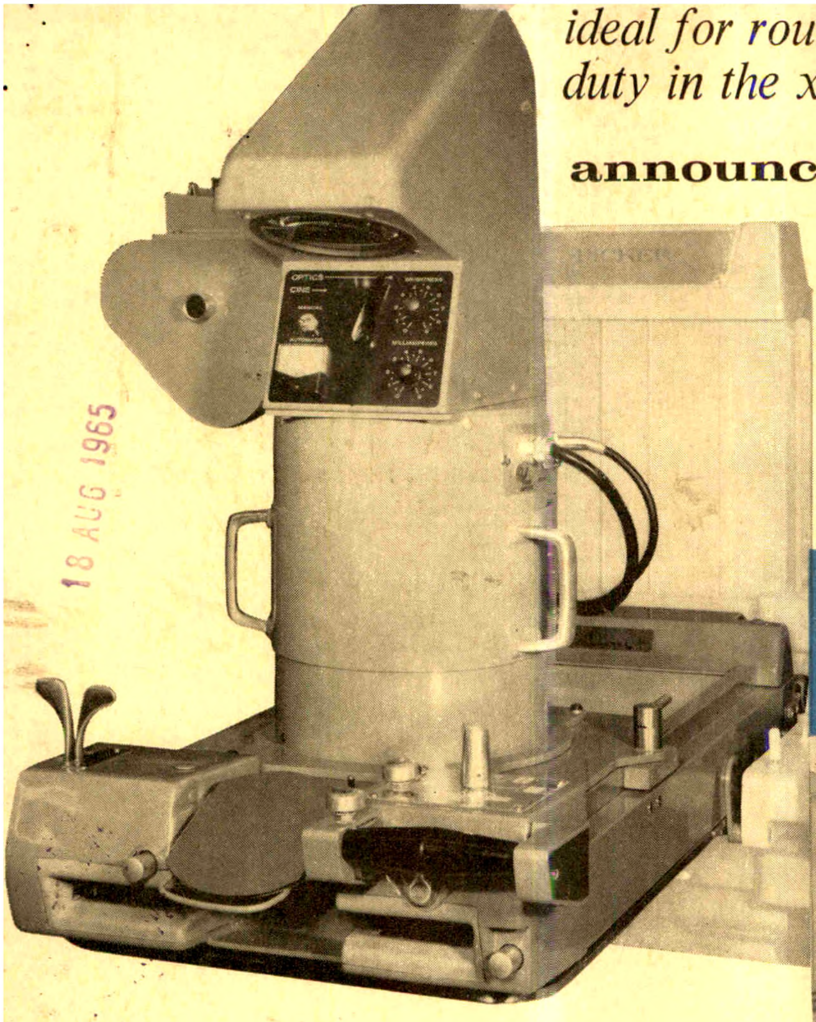

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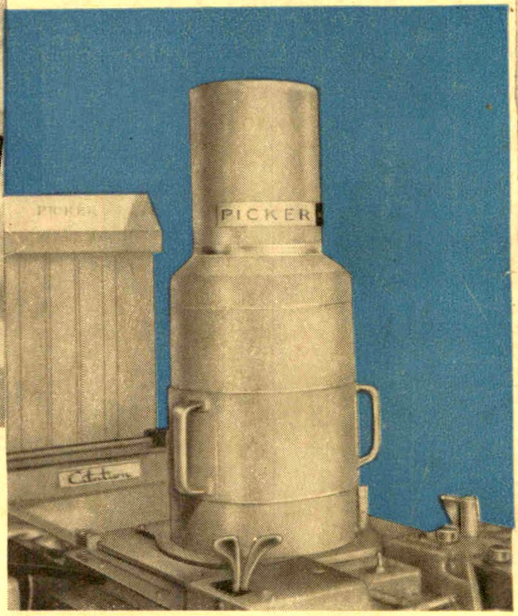

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